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A SYSTEMATIC STUDY OF THE ACTION OF DEFINITELY RELATED CHEMICAL COMPOUNDS UPON ANIMALS.

BY WOLCOTT GIBBS, M. D., *Rumford Professor (Emeritus) in Harvard University*, AND EDWARD T. REICHERT,[1] M. D., *Professor of Physiology in the University of Pennsylvania.*

(Continued from p. 379, Vol. XII.)

Phenylhydrazine Chlorhydrate.

In the frog, phenylhydrazine produces a diminution of sensation and reflex action, loss of voluntary motion, unconsciousness, and finally paralysis. The respirations and heart-beats are decreased. Death occurs from respiratory failure, and the heart is finally arrested in diastole. The nerves do not seem to be noticeably affected, the muscles are less excitable to electrical stimulus, and the cerebro-spinal centres are depressed. When given to dogs by the mouth in full doses there ensue, muscular weakness, unsteadiness in walking, depression of sensation and reflex action, nausea and vomiting, and increased rapidity in both pulse and respiration. The blood almost immediately becomes darkened, the mouth and conjunctiva having a marked appearance of cyanosis, which becomes more and more marked as the poisoning

[1] The appointment of Dr. H. A. Hare to the professorship of the Diseases of Children in the University of Pennsylvania obliged him to withdraw from the present investigation. His place has been supplied by Dr. Reichert, who has had exclusive charge of the purely physiological portion of the work remaining to be done.

progresses until the blood is almost black. The bodily temperature is lowered from 1° to 2° C. If a fatal dose was administered the weakness becomes profound, convulsive movements sometimes occur, sensation and reflex action disappear, the urine and feces are involuntarily voided, there is absolute muscular relaxation, respiration becomes slow and difficult, the pulse is weak, and finally death ensues from cardiac and respiratory paralysis.

When injected into the jugular vein in doses of 0.3 to 0.6 gram the arterial pressure is unaffected, the pulse is sometimes permanently decreased at once, and at others is decreased for a few minutes and then increased. The respirations are increased from one-half to three times the normal number. The blood is greatly darkened. After repeated injections of such quantities, the blood-pressure is invariably slowly and gradually diminished; the heart-beats are generally enormously increased in number, and the respirations are similarly affected. Death occurs in from fifteen to forty minutes, usually from heart-failure, although the respiration is profoundly affected and death may result from a cessation of this function or from a simultaneous arrest of both. If a single dose of from 1 to 1.5 grams is injected the pressure is immediately diminished, the heart-beats are enormously increased and very feeble, and death results in a few minutes.

The diminution of blood-pressure and the increase in the pulse are both due to a direct action on the heart, because the same changes are observed after the isolation of this organ from the nerve-centres, and as the fall of pressure is concomitant with the increased feeble pulse, the two changes progressing together. The increase in the pulse is not dependent on a depression of the inhibitory ganglion, since, even late in the poisoning, weak stimulation of the vagi causes marked inhibition; moreover, the more rapid beats are accompanied by lessened work, and are, therefore, significant of a direct depressant action on the heart-muscle. The increase in the number of respirations is present equally well after section of the pneumogastric nerves, and, consequently, is the result of an action on the respiratory centres. Whether this is direct or indirect through the action of the altered blood is also doubtful. Late in the poisoning, however, these centres are depressed, and may succumb before the heart.

The fatal dose in the dog when given by the mouth is from 0.20 to 0.25 gram to the kilo; when by the jugular vein, from

0.12 to 0.2 gram to the kilo. The fatal dose in the frog is about 0.0003 gram to the gram.

Ortho-tolylhydrazine Chlorhydrate.

In the frog this substance produces a diminution of sensation, loss of voluntary motion, slowing of the respirations and the pulse, and finally complete general paralysis. The nerves when tested by proper means do not seem to be appreciably affected, but the muscles are less irritable. The toxic actions are centred on the brain and spinal cord. Death results from a failure of respiration, and the heart is arrested in diastole.

When given to the dog by the stomach in doses of from 0 5 to 0.7 gram to the kilo of body-weight, it causes weakness, unsteadiness in walking, nausea and vomiting, bluish discoloration of the mouth and conjunctiva, and slight depression of sensation and reflex action. Bodily temperature is lowered; the respirations are increased, but towards the last they are slow, deep and difficult; the heart's action is slower and weak; convulsive movements of a clonic and tonic character occur; paralysis deepens; there is involuntary micturition and defecation; and death ensues from respiratory or cardiac failure. The heart is arrested in diastole, and the blood is almost black.

When injected into the jugular vein in doses of from 0.25 to 0.5 gram there is observed a slight increase in blood-pressure, which is usually accompanied by an unimportant increase in the pulse-rate. The respirations are unaffected or a little accelerated. After repeated doses, both pressure and pulse show a decided downward tendency, and the respirations become greatly increased. The arterial blood at this time is very dark, owing to the action on the hæmoglobin. As death approaches the respirations are diminished, the heart's action is very feeble, the pressure almost at zero, and finally death results from cardiac and respiratory paralysis. The alterations in both blood-pressure and pulse are observed even after the isolation of the heart from the nerve-centres, and as the changes in one are accompanied by corresponding alterations in the other, they must both be due to a direct action of the poison on the heart. The respiratory effects occur just the same after section of the pneumogastric nerves, and are therefore dependent upon an action on the respiratory centres. It is doubtful whether the poison acts directly on the respiratory

centres or not. The alterations in the blood are so profound that the increased respirations may be the indirect effect of the deficient oxygenising power of the red-blood corpuscles. The respiratory centres are, however, ultimately paralysed, as are all the nerve-centres.

The fatal dose in the dog when given by the mouth is from 0.3 to 0.5 gram to the kilo of body-weight; when by the jugular vein, from 0.2 to 0.3 gram to the kilo. The fatal dose in the frog is about 0.0003 to the gram of body-weight.

Para-tolylhydrazine Chlorhydrate.

The actions of para-tolylhydrazine are identical with those of the ortho salt, the only important difference being in a greater intensity of action of the former. The lethal dose was not accurately determined, but it is a little less than that of ortho-tolylhydrazine.

Summary of the Physiological Actions of the Hydrazines.

These substances all possess the same physiological actions in common. They powerfully affect the blood, converting the hæmoglobin into some abnormal form, and thus seriously interfere with the function of the red corpuscles as oxygen-carriers, which in turn acts as a depressant to all forms of vital activity and gives rise to a marked appearance of cyanosis; they depress the cerebro-spinal centres, causing loss of consciousness, sensation, and reflex action; they lower the bodily temperature, doubtless to a large extent by affecting the blood; they are all convulsants, yet relatively feeble in this respect; they all lower the blood-pressure and increase the pulse by a direct action on the heart; they arrest the heart in diastole; they increase the respirations and finally diminish them by primarily stimulating and secondarily depressing the respiratory centres; and they all cause death by cardiac and respiratory paralysis.

In point of general toxicity ortho-tolylhydrazine is least powerful, para-tolylhydrazine slightly more so, and phenylhydrazine half again more poisonous. These substances rank similarly in their actions on the heart, but the reverse is the case as convulsants, phenylhydrazine being feeble and para-tolylhydrazine the most potent. In a majority of cases with the tolylhydrazines the respiration will fail before the heart, but with the phenylhydrazines the heart will usually succumb first.

Toluylene-diamine.

After the injection of this substance into the posterior lymph-sac of the frog the animal soon exhibits signs of general depression: volitional movements become weakened, the legs are relaxed, the frog lies upon his belly, and, if placed on his back, makes no attempt to turn over, the motor reflexes are diminished and finally lost, respiratory movements cease, and the heart is arrested in diastole. The muscles are depressed, the sensory and motor nerves are not appreciably affected, and the loss of reflex excitability is due to an action on the spinal cord.

When administered to dogs by the mouth in the dose of 0.4 to 0.5 gram to the kilo of body-weight, there are observed: salivation, secretion from the nose, sneezing, retraction of the mouth with each inspiration suggesting difficult respiration, the tongue and gums are cyanotic, muscular movements are weakened, the heart-beat is more frequent and feeble, the respiratory movements may at first be increased but are always finally gradually diminished, the bodily temperature is lowered decidedly, the animal whines or howls occasionally as though in pain, the motor reflexes are greatly lessened, voluntary motion is lost, vomiting may occur, the reflexes are finally lost, and death ensues from a failure of respiration within from four to six hours after the dose.

Autopsies show that the blood is bluish-black, that the heart is arrested in diastole and full of dark clotted blood and unirritable, and that the stomach and intestines are greatly congested.

The subcutaneous injection of the drug gives rise to similar results during life and after death. Doses of a little over one half the quantity given above may prove fatal within twenty-four hours, the animals being profoundly affected for two or three hours, then recovering markedly, only to die later, apparently from gastro-enteritis.

Graphic records obtained of the actions on the circulation and respiration by means of the kymographion show that doses as small as 0.08 gram to the kilo injected intravenously are capable of increasing the pulse-rate, pressure and respiration. After doses of about 0.1 to 0.2 gram to the kilo the pulse-rate is variously affected, sometimes being unchanged, at others decreased, followed by a rise, and at others increased at once. After repeated doses the pulse is always increased. The effects on the pressure

are also variable, the general tendency at first being to cause a rise and afterwards a decline. The respirations after such doses are always increased. After repeated injections all three finally fail, death resulting from an arrest of respiration, but the heart is seriously depressed and arrested in diastole.

After section of the vagi and the upper cervical portion of the spinal cord the changes in the circulation are precisely the same as in normal animals, showing, therefore, that the effects on the pulse and pressure are due to direct actions on the heart. The primary increase and final decrease in the respiration-rate are observed after section of the pneumogastric nerves, and are, as a consequence, dependent upon actions on the corresponding centres.

The minimum lethal dose in dogs, when given subcutaneously, is from 0.2 to 0.3 gram to the kilo. Much larger quantities may be intravenously injected without causing immediate death.

Di-nitro-phenol.

When di-nitro-phenol is injected into the jugular vein of a dog in the dose of from 0.01 to 0.17 gram to the kilogram of body-weight, very marked and powerful stimulation of the vagi nerves always occurs, causing a very slow pulse with full systolic waves. This stimulation of the vagi is in direct ratio to the amount of the drug given, and seems to vary slightly with the susceptibility of the individual animal. Following this stage, if the dose has been as small as from 0.01 to 0.025 gram to the kilo, there comes a period of increased pulse-rate of a not very marked character, accompanied by a rise in blood-pressure.

These changes occur in both curarised and non-curarised animals, and are constant. We have further proved by repeated experiments that the slow pulse is due to vagal stimulation of a centric nature, since it is at once put aside by section of these nerves, the pulse-rate becoming as rapid as in the normal dog under such circumstances.

When as much as 0.170 gram to the kilo is injected into the jugular vein, the heart stops before respiration ceases, becoming slower and slower, until finally the arterial pressure also begins to fail and death occurs. Death is produced by as little as 0.05 gram to the kilo.

When di-nitro-phenol in the dose of 0.3 gram to the kilo is

given to a full-grown dog by the mouth in 40 cc. of water, vomiting comes on in from 5 to 10 minutes, which soon rids the stomach of the drug. For this reason the exact dose necessary to produce the symptoms which follow cannot be stated. The tongue is protruded and saliva drips from the mouth and from the end of the tongue; the respirations are greatly increased, becoming exceedingly frequent, as high as 180 per minute, but full and forcible, the chest-walls being distended to the utmost at each breath. The head is extended to straighten the windpipe, the pace is slightly staggering, and the hind legs are a little more affected than the fore. Consciousness is entirely preserved. The pupils are widely dilated, the temperature in the rectum rises from 2° to 3° C. Thirst soon becomes severe, probably owing to the rapid respirations. Death ensues in a half an hour, the respirations suddenly becoming slower and slower, then ceasing at once. After death *rigor mortis* appears immediately. Sometimes the urine and feces are passed involuntarily late in the poisoning. The urine is colored yellow, probably from the drug.

When 0.166 gram is given for each kilogram the symptoms are identical with those just stated, except that death is put off for one hour and a half. Shortly before death the animal emits a few howls, walks around the room, and then lying down suddenly ceases breathing. The heart at first is slowed in its beat, afterwards the action becomes very rapid, finally reaching 190 a minute. It was noted that respiration stopped before the heart.

When di-nitro-phenol in the dose of 0.015 gram is given to a frog weighing 80 grams, the drug being injected into the posterior lymph-sac, the hind legs seem to have their power slightly decreased, but rapidly recover their normal tone after a few minutes. Soon after this, about fifteen minutes following the injection, muscular power progressively diminishes, and the animal, when placed on his back, has great difficulty in regaining his proper position. Twenty minutes after the dose was given the frog is very much relaxed and appears half dead, so that he will lie in any position in which he is placed. Every portion of the body is discolored by the poison. Five minutes later the reflexes are still intact. Respiration ceases, and on exposing the chest at this time the heart is found to be acting with a remarkable degree of slowness, the diastole being long and the relaxation great. The blood is seen to be dark and grumous. Forty minutes after the drug

was given the beat is only 10 or 12 per minute, and the animal, now having lost all reflexes, is to all appearances dead, save for the occasional heart-beat. The question at once arises as to the cause of the failure of motor power and the subsequent loss of reflex activity. In order to determine whether the drug acts on the spinal cord, or on the nerves, or muscles, the artery of one hind leg was tied, thus preventing the access of the poison to the part thus supplied by the vessel, and the drug was then injected into the posterior lymph-sac. As the minutes pass by it is noted that the reflexes remain equal in both the protected and unprotected legs, which is followed by a loss of power in the entire body, with a complete loss of reflex activity in all parts alike. Respiration has ceased. No response can be obtained by any form of mechanical or chemical stimulus. On opening the chest the heart will be seen beating only about once a minute, and finally only the auricles contract.

This substance must act upon the spinal cord, and its action is doubtless chiefly on the motor portion, for the reasons that there is an equal failure of power in both protected and unprotected legs, which would not be the case if the action were peripheral; and because the impulses arising from peripheral irritation seem readily carried up the sensory part of the cord at a time when the general condition is one of profound muscular relaxation.

It is worthy of note that death occurs from respiratory failure if the dose be slowly absorbed as when given by the stomach, but from heart-failure if it be injected into the jugular vein in a single dose.

Tri-nitro-phenol.

When about 0.06 gram of this substance to the kilogram of the dog's weight is injected into the jugular vein there immediately ensues an extraordinary stimulation of the pneumogastric nerves or centres, so that the heart is within a few seconds completely arrested. At this time, however, section of these nerves restores the cardiac action, so that it would seem that the action of the drug is upon the central portion of the inhibitory apparatus of the heart. It is evident, however, that the peripheral portion is also acted upon, because the normal rate is not restored. This is corroborated by the fact that atropine, if injected at this time, fails to increase the rate at all. Tri-nitro-phenol seems to prevent the action of atropine on the ends of these nerves. Along with

the slowing of the heart's action there is a slight and constant fall of arterial pressure. If the dose be only 0.03 gram to the kilo these effects are less marked.

Upon the respiration the drug acts as a depressant, a dose of 0.06 gram to the kilo being fatal in this way. As a consequence, should further studies be necessary the animal must be kept alive by artificial respiration.

When 0.00001 gram to the gram is given to a frog and injected into the posterior lymph-sac, it causes a slight increase in the reflexes, which is accompanied by a slowing of the heart. If the dose equals as much as 0.000017 gram to the gram these symptoms are somewhat increased, and death ensues many hours afterwards from respiratory failure. If the dose is increased to 0.00005 gram to the gram the reflexes are at first increased, then diminished, and simultaneously the respiratory movements become much embarrassed and slowed, death eventually resulting from respiratory paralysis. The pulse is also much slower. After 0.0001 gram to the gram is given, absolute and complete paralysis comes on, and there is no stage of increased reflex activity as occurs with smaller doses. After death the nerves and muscles respond more feebly to electrical stimulation than normal. The minimum fatal dose of tri-nitro-phenol is 0.000015 gram to the gram of the frog, death being due to respiratory paralysis accompanied by cardiac depression.

Erb found that the daily use of a grain of this substance for ninety days in a rabbit produced yellowness of the conjunctiva, of the inner surface of the ear, and of the urine, with an occasional slight diarrhœa and great loss of weight, without any elevation of temperature. After a time the animal seemed to grow accustomed to the poison, so as to regain in great measure its flesh. Three grains a day caused, in about two weeks, the death of the rabbit, with symptoms of inanition. All the tissues, except the nervous, were stained of an intense reddish color, as was also the urine. Eight grains produced a fall of temperature, weakness, diarrhœa, collapse and death, sometimes preceded by tremblings and even by convulsions, in about twenty-three hours. The most remarkable physiological effect of the poison occurred in the blood. The blood of animals slowly killed by the poison was of a dirty brown color, with distinct nuclei both in the red-blood disks and floating free in the serum. Dr. Erb found that this alteration

occurred during life, and was accompanied by a decided increase in the number of white corpuscles. These changes in the blood were apparently the cause of death, and seem to have been due, so far at least as concerned the red disks, to a direct action, for Erb found that identical, or very similar alterations took place when the blood was mixed with the picrate of sodium outside of the body.

Erb found picric acid to act on man as on the lower animals. Twenty-four hours after the ingestion of fifteen grains of it the yellow color was plain in the conjunctiva, the skin and urine. The temperature was not elevated, and gastric disturbance was usually absent, but sometimes it was severe. As in animals, so in man, picric acid was found abundantly in the urine. A teaspoonful produced no more violent symptoms in man than bad vomiting and purging.[1]

Summary concerning the Actions of the Nitro-phenols.

Ortho-nitro-phenol kills by cardiac arrest when given by the jugular vein, and by respiratory failure when administered by the mouth. Death is produced by 0.1 gram to the kilo of body-weight. The cardio-inhibitory apparatus is stimulated centrally and peripherally.

Meta-nitro-phenol kills by cardiac failure when given by the jugular vein, and by respiratory paralysis when by the mouth. Death is produced by 0.083 gram to the kilo by the jugular vein. The cardio-inhibitory apparatus is stimulated the same as by the ortho compound.

Para-nitro-phenol is fatal by heart-failure when given by the jugular vein, and by respiratory arrest when by the mouth. Death is produced by 0.01 gram to the kilo by the jugular vein. The cardio-inhibitory centres and peripheries are stimulated by small doses, but large doses paralyse them.

All three affect the nervous system, slightly depressing it.

Di-nitro-phenol kills by heart-failure when administered by the jugular vein, and by respiratory paralysis when by the mouth. Death is caused by 0.05 gram to the kilo by the jugular vein. It powerfully stimulates the cardio-inhibitory apparatus. The nervous system is depressed in its motor portion.

Tri-nitro-phenol kills by respiratory failure unless the drug is thrown into the circulation in large amount *en masse*, when it

[1] Wiener Med. Presse **23**, 1526.

arrests the heart. Death is produced by 0.06 gram to the kilo when injected by the jugular vein. It stimulates the cardio-inhibitory centres with extraordinary power.

Nitro- and Di-nitro-benzol.

Nitro-benzol.—In the frog this substance induces a brief period of reflex excitability, during which convulsive movements may occur; this is followed by weakness and gradual loss of reflex excitability. The respirations and heart-beats are increased, voluntary movement is soon abolished, the respirations cease, and finally the heart succumbs. Convulsions rarely occur, and when present are of spinal origin. The sensory and motor nerves and muscles are little, if at all, affected, so that the changes in reflex excitability are of spinal origin. The blood is of a chocolate color.

When administered to the dog by the stomach, in the dose of 0.5 to 0.75 gram to the kilo of body-weight, there is observed, salivation, vomiting, decided restlessness, unsteadiness in walking and other movements, staggering, tremors, delirium, an increase of temperature, a rapid pulse, and an increase in the respirations. As the toxic actions progress, weakness in the legs is marked, the animal is unable to stand, and crawls upon his belly or lies upon his side, making ineffectual attempts to get on his feet. Unconsciousness supervenes, the dog barks, whines or howls occasionally, and convulsive movements may occur of a clonic and tonic character. If vomiting has not been observed, the climax of the toxic action is reached within two hours, and apparent recovery occurs in from four to six hours. Should the dose be as large as 1 gram to the kilo, the dog gradually passes into a condition of paralysis of all the functions, the circulation fails, the blood may be more or less chocolate-colored or unaffected, the respiratory centres are depressed, and death results from their paralysis. The alterations in reflex excitability and the convulsions are due essentially to a direct action on the spinal cord.

The degree of poisonous action does not depend regularly upon the size of the dose, the same proportionate quantity in different animals causing wide variations in the intensity of action. Moreover, doses sufficient to cause marked and immediate effects when given by the stomach, are practically inert when injected subcutaneously. Even as much as 0.75 gram to the kilo may thus be given without other obvious effects than a slight increase of the

pulse, slight tremors, and restlessness. Doses of 2 grams to the kilo subcutaneously may elicit within six hours no other symptoms, the toxic actions progress very slowly, and the animal passes into a moribund condition, and may remain this way for twenty-four hours or more before death ensues.

When injected into the external jugular vein in doses of 0.5 to 1 gram the arterial pressure is diminished, and the pulse and respirations increased. Repeated doses lower the pressure more and more, the increase of the pulse is followed by a decrease, but the respirations tend to become greatly augmented. The increase in the heart-beats is usually trifling and transient, although in some cases it persists until death. Both the increase and decrease in the pulse indicate cardiac depression, since both occur after the isolation of the heart from the nerve-centres, and as they are always accompanied by lowered arterial pressure, which is in part independent of any vaso-motor action. While the fall of arterial pressure is chiefly due to a depression of the heart, the vaso-motor centres in the medulla oblongata are also involved, since this effect is not as decided after their destruction. The changes in the respirations are due to a direct action on the respiratory centres, because they are observed equally well after section of the par vagum. The blood may not in the least be discolored unless the action of the poison has extended over several hours, but the spectroscope invariably shows the presence of nitrite-hæmoglobin.

Death invariably results from a failure of respiration, although the circulation and other important functions are seriously depressed.

The lethal dose in the dog by the stomach is from 0.75 to 1 gram to the kilo of body-weight; and by the vein, from 0.15 to 0.25 gram to the kilo in divided doses. Absorption takes place so slowly from the subcutaneous tissues, or for some other obscure reason, that the fatal dose by this means is disproportionately large.

Di-nitro-benzol.—The physiological actions of this substance do not, as a whole, differ essentially in character from those of nitro-benzol, save in intensity. This preparation is more apt to cause vomiting; it is rapidly absorbed from the subcutaneous tissues, and is consequently quickly poisonous when given in this way; its action on the respiratory centres is very feeble as a stimulant but strong as a depressant, so that the respirations are usually but

little increased and generally notably decreased; the actions on the spinal cord are far more pronounced, the alterations in reflex excitability are more decided, and convulsions are almost invariably observed which are of a strong tetanic nature; the heart and vaso-motor centres are more depressed; the blood is always greatly discolored, and so marked is this in comparison with what is observed in poisoning with nitro-benzol, that one generally can tell simply by the color of the blood which substance was used—in poisoning from nitro-benzol the blood may not in the least be discolored, but even small doses of di-nitro-benzol will make themselves strongly manifest in this way; finally, it acts more promptly and powerfully, and is lethal in smaller doses.

Amides.

Formamide.—In the frog this substance causes a diminution of sensation, muscular twitchings, clonic convulsions followed by those of a tonic character, paralysis, and finally death from respiratory failure. The sensory and motor nerves do not seem to be affected, for they retain their irritability long after death. The convulsions, as well as the diminution of sensation, are due to actions on the spinal cord.

When given to the dog by the mouth it so readily produces vomiting that the drug is ejected before any definite symptoms are developed. If injected subcutaneously in doses of 2 grams to the kilo of body-weight, it gives rise to restlessness and signs of pain, which are evidently due to the local irritation caused by the formamide. Vomiting is apt to occur, the bodily temperature is diminished, and the pulse somewhat slower.

When injected into the jugular vein in doses of from 0.2 to 0.3 gram to the kilo there is a momentary fall of blood-pressure, but no decided change in the pulse-rate. This diminution, which amounts to from an eighth to a fourth of the normal pressure, is followed in a few moments by a recovery, so that the normal is attained within about thirty seconds. The pressure continues to increase, and it may reach from ten to forty millimeters in excess of the normal. This increase is accompanied by a marked slowing of the pulse and vigorous heart-beats. The pressure gradually returns to the normal, but the pulse continues at a lessened rate. The respirations are also slower. When these doses are repeated similar results follow each injection, until after awhile the pressure

is permanently lowered, the heart's action excessively slow and strong, the respirations decreased, and death results from paralysis of respiration. When larger doses are given the circulatory and respiratory changes are intensified.

The slowing of the pulse is due to a stimulation of the cardio-inhibitory centres in the medulla oblongata, since it is not observed after section of the vagi. At the approach of death the heart-beats are also decreased, but this is of cardiac origin, because it is present even after the isolation of the heart from the nerve-centres. The changes in blood-pressure are essentially vaso-motor, and due to a direct action on the capillaries. This is evident in the facts that they occur after the destruction of the vaso-motor centres in the medulla oblongata and the separation of the heart from the nerve-centres, and as they are not accompanied by corresponding alterations in either the number or character of the heart-beats. The slowing of the respirations is the same after the pneumo-gastric nerves are cut, and is, therefore, the result of a depression of the respiratory centres.

The fatal dose in the dog when given by the jugular vein is from 1.5 to 2 grams to the kilo of body-weight. In the frog the fatal dose is about 0.0003 gram to the gram.

Acetamide.—Upon the frog, acetamide in the dose of 0.0005 gram to the gram causes great quietude, relaxation, and depression of respiration. If the dose be as large as 0.001 gram to the gram these symptoms are followed by an increase in reflex action, and then by convulsions of a tetanic type which are of spinal origin.

Given to the dog by the mouth in the dose of 0.5 to 0.7 gram to the kilo it is likely to cause vomiting, but no other troubles. Even doses of 2 grams to the kilo are without important effects.

When injected directly into the circulation in doses of from 3 to 5 grams the pressure is slightly increased, the pulse lowered from ten to twenty beats, and the respirations a little increased. These doses may be repeated until the animal receives a quantity equal to 3 grams to the kilo without increasing the pressure more than ten millimeters and the respirations more than one-third, or diminishing the pulse more than one-fifth. The slowing of the pulse we have determined to be due to a stimulation of the cardio-inhibitory centres.

These large doses seem to cause pain when they are injected, and also induce more or less struggling. After a time there is

produced extreme drowsiness or deep sleep. The animal's temperature does not appear to be affected.

The lethal dose for the dog is not known to us, but it is more than 5 grams to the kilo. The fatal dose in the frog is about 0.002 gram to the gram.

Propionamide.—When given to the frog in the dose of 0.004 gram to the gram, loss of voluntary movement rapidly ensues, and this is followed by tetanic convulsions. The nerves and muscles readily respond to stimulus long after death. The convulsions are spinal.

When given to the dog by the stomach or jugular vein, the animal being free to run about, it produces no symptoms other than a slight increase in the respirations and a slowing of the pulse. Doses as high as 0.5 gram to the kilo are thus ineffectual. When the dose is 0.05 gram to the kilo by the vein no change in arterial pressure occurs, and the pulse is not affected in either rate or force. Even if the dose amounts to 0.125 gram to the kilo there is little effect, but if it is as much as 0.25 gram to the kilo the pulse is much slower and the beat decidedly stronger, and the blood-pressure is increased. The decrease in the pulse we have found is due to a stimulation of the cardio-inhibitory centres.

The fatal dose in the frog is about 0.0005 gram to the gram.

Benzamide.—Upon the frog in the dose of from 0.003 to 0.005 gram to the gram it causes a diminution of sensibility and reflex action, loss of voluntary movement, and paralysis. The nerves and muscles do not seem to be affected, but the spinal cord is certainly depressed.

If administered to the dog by the mouth in the dose of 0.8 gram to the kilo of body-weight it induces staggering, salivation, vomiting, muscular weakness, diminution of sensibility and reflex action, a lowering of bodily temperature from 1° to 3° C., an increase in the respirations, a decrease in the pulse, profound relaxation, and unconsciousness. If the drug has not been lost by vomiting the pulse becomes feeble, the respirations slow, and death results from a failure of respiration.

When injected into the jugular vein of the dog in doses of 0.5 gram to the kilo the blood-pressure rapidly declines for about thirty seconds until it reaches a point fifty or sixty millimeters below the normal; the pulse at the same time is more frequent and the force of the heart-beat lessened, and the respirations are

increased in frequency and depth. The pressure, when it reaches its lowest point, immediately begins to recover; the pulse at the same time becomes slower and in a few minutes is less than normal, but the force of the heart is increased, although not sufficient to restore the normal pressure; and the respirations are slower and deeper. When this dose is repeated similar results ensue from each injection until the pressure is permanently lowered almost to zero. Even now several doses may be given before the heart is paralysed. Three doses are sufficient to abolish completely all sensation and to dilate the pupils. Death usually results from a failure of respiration.

The alterations in the pulse-rate are observed after the isolation of the heart from the nerve-centres, and are, therefore, due to a direct action of the poison on the heart. The diminution of blood-pressure we have found is owing to a depression of the heart, and to a similar condition of the medullary vaso-motor centre. The primary increase and final decrease in the respirations are due to stimulation and subsequent depression of the respiratory centres.

The fatal dose in the dog by the mouth is from 0.7 to 0.8 gram to the kilo of body-weight; by the jugular vein, from 0.5 to 0.6 gram to the kilo. The lethal dose in the frog is about 0.001 to 0.003 gram to the gram.

Oxamide.—This substance when given to dogs by the mouth in quantities as large as 5 grams to the kilo of body-weight is absolutely without any apparent action.

Sulpho-carbamide.—Twenty grams in divided doses were injected within twenty minutes into the jugular vein of a dog weighing 10 kilos, without producing other effects than a slight diminution of the pulse and a trifling increase in the respirations.

Pyromucamide.—This compound failed to produce any toxic symptoms in a dog weighing 7 kilos, after the intravenous injection of 30 grams in divided doses, within three-fourths of an hour. We are indebted to Prof. Henry B. Hill for the preparation employed.

Anilides.

Formanilide.—In the frog this substance causes a loss of voluntary movement, heightened reflexes, convulsions, and peculiar muscular tremblings. Sensibility and the reflexes are finally diminished, and general paralysis ensues. The muscles and nerves retain their irritability after death, but they are less excit-

able than normal. The spinal cord is first stimulated and then depressed. The convulsions are spinal.

When given to the dog by the mouth, or subcutaneously, there is noted general feebleness, languor, quickening of the respirations, an increase followed by a decrease of the pulse-rate, and sleep which deepens into stupor from which the animal can be aroused only with some effort. The reflexes are increased, a loud noise, or a blow upon the table, will bring on muscular movements of an unco-ordinated type. The patellar reflex is augmented; salivation is sometimes present; the temperature is lowered from 1° to 2° C., and slight convulsions are often observed. Should the dose be fatal, sensibility and the reflexes are diminished, the respirations are decreased in frequency, the heart's action becomes slower, the animal passes into a condition of collapse, and death results from a failure of respiration.

When the carotid artery is connected with the kymographion and the drug is given by the jugular vein in the dose of 0.06 gram to the kilo, the pulse is for a few moments increased and then diminished, and the arterial pressure is a little depressed. If the dose is as large as 0.1 gram to the kilo the pulse-rate is decreased and the pressure is slightly lowered. When this dose is several times repeated the slowing of the pulse gives place to an increase which exceeds the normal, but the pressure is more and more diminished. The respirations are quickened. Finally, as death approaches the heart-beats become slower and slower, although the pulse-curves are high and indicate that the viscus is far from being exhausted; the pressure is gradually lowered to zero; the respiratory movements become very slow, and death results from the cessation of respiration.

The primary decrease of the heart-beats we have found to be due to a stimulation of the cardio-inhibitory centres and ganglion; the frequent pulse, to their depression; and the slow pulse late in the poisoning, to a direct action on the heart. The fall of pressure is dependent almost solely upon a depression of the vaso-motor centres in the medulla oblongata, but the alterations in the heart-beats are also in part accountable. The changes in the respirations are due to a direct action on the respiratory centres, consequently the centres are first stimulated, then depressed. Death occurs from respiratory paralysis.

The fatal dose in the dog when given by the mouth is from 0.4

to 0.5 gram to the kilo of body-weight; when by the jugular vein, about 0.4 gram to the kilo. The lethal dose for the frog is about 0.0008 gram to the gram.

Acetanilide.—When this substance is given to dogs by the stomach, vomiting is so readily produced that it is only by repeated doses that a full toxic action can be studied. Doses of 0.5 gram to the kilo of body-weight cause salivation, vomiting, weakness, a lowering of the temperature from 0.3° to 0.8° C., an increase of the pulse, and a slight increase in the respirations. After repeated doses the weakness becomes marked, the animal is very sleepy, the temperature steadily falls, the pulse becomes weak and increased in frequency, tremors and convulsive movements occur, the blood is darkened, and the respirations are shallow and slower, and finally cease.

When injected directly into the circulation in doses of from 0.3 to 0.6 gram, the arterial pressure is lowered about 10 mm., and the pulse and respirations are increased in frequency. Repeated doses continue to lower the pressure; the pulse for a time is more and more increased, but after about the third dose, reaches its maximum and begins falling, steadily declining until death ensues. The respirations, however, show no tendency at any time during the progress of the poisoning to go below the normal until immediately before death, and are generally increased about two or three times the normal rate.

Doses as large as from 2 to 4 grams lower the pressure and pulse-rate and increase the respirations. After a dose of 2 grams the pressure will fall immediately about 20 mm., and gradually recover during the following fifteen minutes. The pulse is reduced about twenty per cent., and the respirations are doubled in frequency. Repeated doses of this size act more powerfully on the pressure than the first dose, but the effects on the pulse and respirations are not as marked. Even as much as 4 grams may be injected in a single dose without profoundly affecting the circulation.

After the isolation of the heart from the nerve-centres and the destruction of the vaso-motor centres in the medulla oblongata, the same changes in the pulse and blood-pressure ensue, so that these phenomena are of cardiac origin. The increase in the respirations is as well marked after section of the vagi as before, and is therefore due to an action directly on the respiratory cen-

tres. The blood is discolored, owing to the presence of methæmoglobin. Apart from a pronounced destructive action on the hæmoglobin and the consequent interference with functions of the red-blood corpuscles, acetanilide is certainly a feeble poison.

Death results from a failure of the respiratory centres.

We have not been able to determine the exact fatal dose in the dog when the drug is given by the stomach, but by the vein the lethal quantity in divided doses varies from 0.3 to 1.2 gram to the kilo of body-weight.

Benzanilide.—This substance may be given to dogs by the stomach in quantities as large as 5 grams to the kilo without inducing other obvious symptoms than a slight decrease in the animal's temperature.

When injected into the jugular vein in doses of 0.3 gram it temporarily slightly increases the arterial pressure, the pulse and the respirations, and lowers the temperature. A number of such doses may be given for a time, always causing a repetition of these effects, but finally the pressure and pulse show a downward tendency, while the number of respirations is increased. Although the actions on the circulation are far from being decided, there comes a time sooner or later when one of these doses will in a few seconds paralyse the heart. The effects on the circulation appear equally well after the isolation of the heart from the nerve-centres, and consequently are of cardiac origin. The alterations in the respirations are due to direct actions on the respiratory centres.

Benzanilide is in the form of fine micaceous crystals which are very insoluble, so that how far these effects are due to peculiar physiological properties of the drug *per se* is doubtful, but the absence of similar symptoms in animals after having been given such enormous doses by the stomach, certainly justifies the conclusion that the effects following its injection into the circulation are due to the mechanical actions of the undissolved particles clogging up the capillaries in the important centres.

(*To be continued.*)

Contributions from the Laboratory of General Chemistry, University of Michigan.

II.—THE CONSTITUTION OF ALIPHATIC KETONES, AND THE ACTION OF SODIUM ON ACETONE.

By Paul C. Freer.

Aliphatic ketones, in which the carbonyl group is attached to one or more negative groups of atoms, have been known for some time, and have since their discovery been a fruitful topic of discussion. It was in 1863 that Geuther[1] published his first paper on the action of sodium on acetic ether, by this means preparing sodium aceto-acetic ether, $CH_3.CO.CHNa.COOC_2H_5$, which, when heated with methyl or ethyl iodide, yielded the corresponding alkylated derivatives of that substance. The discussion concerning the constitution of this interesting body has gradually drawn into the field of study the nature of other ketones and ketone-like substances which, similarly to aceto-acetic ether, give sodium derivatives on treatment with sodium or sodium ethylate.

The question as to the constitution of the ketones themselves has been intimately connected with that of their sodium derivatives, for chemists were divided in their opinion as regards the nature of these substances. Many, with Geuther as their chief representative, maintained that to possess acid properties these ketones must contain an hydroxyl group, just as other organic compounds do which act similarly under similar conditions, and that hence aceto-acetic ether possesses the formula $CH_3.C(OH):CH.COOC_2H_5$, the hydrogen which is connected with oxygen being replaced by sodium in the formation of the metallic compounds. Opposed to this view was that of a large number who thought that more probably the constitution would be represented by the formula $CH_3.CO.CH_2.COOC_2H_5$, and consequently, that, in the sodium derivative, the metal is directly attached to carbon—$CH_3.CO.CHNa.COOC_2H_5$. The latter view was the one held by Frankland and Duppa,[2] who, simultaneously with Geuther, began a research on the action of sodium upon organic ethers. Geuther[3] assumed his formula to be the correct one because aceto-acetic ether had an acid nature (although it does not redden litmus and

[1] Jsb. Chem., 1863, 324. [2] Ann. Chem. (Liebig) **138**, 328; **219**, 119.
[3] Jsb. Chem., 1865, 302.

its metallic compounds are decomposed by carbonic acid). His principal reasons for the theory were, however, based upon Wedel's production of dioxy-terephthalic ether (quinone-hydro-dicarboxylic ether)[1] from dibromo-aceto-acetic ether. As dioxy-terephthalic acid readily yields hydroquinone on distillation, Geuther assumed the presence of two hydroxyl groups in the former, and accordingly, reasoning backward, this, to his mind, necessitated an acceptance of hydroxyl in dibromo-aceto-acetic ether, and therefore in aceto-acetic ether. Geuther advances the fact that dioxy-terephthalic ether readily yields a diacetyl derivative on being heated with acetyl chloride at 50°, as sufficient proof for the existence of two hydroxyl groups in dioxy-terephthalic ether, and the reverse should certainly be taken as an indication of the non-existence of such groups; yet, as I have experimentally proven, there is no reaction between aceto-acetic ether and acetyl chloride under conditions similar to those described by Wedel[2] for dioxy-terephthalic acid, while at higher temperatures acetyl chloride destroys aceto-acetic ether, forming ethyl chloride, carbon dioxide, acetone, acetic ether, and possibly carbaceto-acetic ether, although the analyses given by Wedel[3] are scarcely to be taken as agreeing with anything. Wedel assumes that, as hydrochloric acid must be formed from the acetyl chloride in order to produce these reactions, the hydrogen for the same is necessarily furnished by an hydroxyl group. Under the conditions of the experiment, however, nothing is easier to assume than that acetyl chloride acts as a dehydrating agent: the blackening of the oil referred to by Wedel seems to indicate this. The water so produced could then readily furnish hydrochloric acid. The experiments with acetyl chloride, then, not only fail to prove the presence of an hydroxyl group in aceto-acetic ether, but seem, indeed, to point toward its non-existence.

That dioxy-terephthalic ether contains two hydroxyl groups, no one will deny; but that fact seems to me to have no bearing upon the constitution of aceto-acetic ether itself. It is possible, however, that the introduction of negative groups in place of hydrogen in aceto-acetic ether, as is the case in the dibromo-aceto-acetic ether, would change the constitution of the substances from that of the true ketone to that of the unsaturated alcohol. Early in the history of aceto-acetic ether, Frankland and Duppa[4] discovered

[1] Ann. Chem. (Liebig) **219**, 74. [2] Ibid. 85. [3] Ibid. 117.
[4] Jsb. Chem., 1865, 304.

that the products of the action of methyl or ethyl iodide upon sodium aceto-acetic ether were decomposed—by heating with water, in a sealed tube, or by boiling with dilute acids—into alcohol, carbon dioxide and *substituted* ketones:

$$CH_3.CO.CHCH_3.COOC_2H_5 + H_2O =$$
$$CH_3.CO.CH_2.CH_3 + CO_2 + HOC_2H_5.$$

Frankland then formulated a reaction destined to once more open a wide field for discussion, explaining the formation of aceto-acetic ether from acetic ether and sodium; assuming the existence of a sodium acetic ether, $NaCH_2.COOC_2H_5$, which, when brought in contact with acetic ether, formed aceto-acetic ether, as follows:

$$CH_3.COOC_2H_5 + CH_2Na.COOC_2H_5 =$$
$$CH_3.CO.CH_2.COOC_2H_5 + NaOC_2H_5.$$

I need scarcely recall that this metallic derivative of acetic ether is as yet purely hypothetical. Lippman[1] strengthened Frankland and Duppa's view by making aceto-acetic ether from acetyl chloride, acetic ether and sodium. The view that in such a substance as acetic ether, sodium could replace hydrogen and attach itself to carbon, was believed in by the majority of chemists, although the sodium acetic ether had never been isolated. The statement is made that sodium does not attack perfectly dry acetic ether, free from alcohol. I dried some of the ether, first by allowing it to stand over night over granulated calcium chloride, which removed the greater part of the water and any alcohol which might have been present; I then boiled the ether for some time in a flask fitted with an inverted condenser, over phosphorus pentoxide, and after diluting with two or three volumes of equally dry ethyl ether, I added powdered sodium. A reaction at once set in, and continued until all of the sodium had disappeared. On filtering the solid formed, drying, and acidifying, there was nothing but aceto-acetic ether produced, showing that, even under circumstances which ordinarily produce these sodium compounds, the sodium acetic ether is converted into aceto-acetic ether. However, as the operation was performed with perfectly dry acetic ether, I cannot see how the acceptance of an intermediary sodium acetic ether is to be avoided. The impossibility of isolating it, however, might be taken as pointing toward a different structure for the methyl group in acetic ether, and for one of those supposed to exist in

[1] Jsb. Chem., 1868, 510.

acetone; and we might be strongly tempted to assume that the facility with which a hydrogen atom in the latter body is replaced by sodium indicates the existence of an hydroxyl group in the same. Geuther[1] believed that the assumption of the existence of sodium acetic ether was unnecessary, for sodium ethylate as well as sodium could produce aceto-acetic ether from acetic ether, as follows:

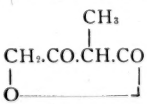
$$2CH_3.COOC_2H_5 + NaOC_2H_5 = CH_3.CO.CHNa.COOC_2H_5 + 2HOC_2H_6.$$

This view being at that time strengthened by the statements of Ladenburg,[2] Oppenheim and Precht,[3] and others, that sodium has very little, if any, action on perfectly-dry acetic ether, free from alcohol. Wislicenus[4] exhaustively reviewed the subject of the constitution of aceto-acetic ether and inclined toward the constitution $CH_3.CO.CH_2.COOC_2H_5$, chiefly because sodium aceto-acetic ether, when acted upon by ethyl or methyl iodide, yielded on saponification acetones substituted with alkyl radicles; and also because the substance is readily reduced to β-oxy-butyric acid by means of sodium-amalgam, while the corresponding unsaturated acid, crotonic acid, is not influenced by this reagent.

$CH_3.COH:CH.COOC_2H_5$. Aceto-acetic ether. $\qquad$ $CH_3.CH.CH.COOC_2H_5$. Crotonic ether.

This latter point seems to me to be well taken; indeed, the behavior of so-called ketones toward reducing agents differs widely.

Some time ago I entered into the study of tetrinic acid, and, as a few of my experiments seem to me to have a bearing on the case, I will introduce them here. The constitution assigned to tetrinic acid by Michael[5] and Cornelius[6] is



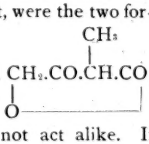
The acid, or its sodium salt, on treatment with phenyl-hydrazine acetate, whether in aqueous or in alcoholic solution, yields a crystalline substance which crystallises in concentric prisms, sparingly soluble in hot water, soluble in hot dilute alcohol, from which it separates on cooling, the melting-point being 191°–192°. On

[1] Jsb. Chem., 1868, 511. [2] Ber. d. chem. Ges. **3**, 325. [3] Ibid. **9**, 320.
[4] Ann. Chem. (Liebig) **186**, 161. [5] J. prakt. Chem. [2] **37**, 503.
[6] Ber. d. chem. Ges. **21**, 2607.

exposure to the atmosphere, as well as on recrystallisation from alcohol, this compound becomes pink, so that slight decomposition caused the nitrogen determination to be inaccurate.

Weight of substance, 0.2239 gram; formula, $C_{11}H_{12}N_2O_2$. *B*, 739.25 mm.; *t*, 20°; N, 24 cc.

	Calculated.	Found.
N	13.70	12.38

The figures, however, show that one formula-weight of phenyl-hydrazine has reacted with one of tetrinic acid. This is all that is at present necessary, for it shows that tetrinic acid, like other ketones, reacts with phenyl-hydrazine. I intend at some future time to investigate the substance more closely. Now, tetrinic acid, according to Demarcay, is not reduced by sodium-amalgam, and I took occasion to repeat his experiments, both in acid and in alkaline solution, in the heat and in the cold, and obtained, in the main, unchanged tetrinic acid, which was rendered impure by a small amount of a thick oil, the quantity of which in all cases was too small to render an investigation of its nature practicable. The result, then, shows that tetrinic acid, if at all reduced, is changed, only with the greatest difficulty, by nascent hydrogen, in which respect it resembles crotonic acid and other unsaturated compounds, and differs from aceto-acetic ether. Yet, were the two formulæ as follows: $CH_3.CO.CH_2.COOC_2H_5$ and  , there could be no reason why they should not act alike. If tetrinic acid be neutralised with sodium hydrate and evaporated to dryness, the sodium salt separates in reniform masses which are easily soluble in water, and which, on crystallising, contain three molecules of water of crystallisation. The salt is best obtained by dissolving tetrinate of sodium in a little water, adding four volumes of alcohol and then mixing the clear solution with an equal volume of ether, when the sodium salt crystallises in shiny plates. The salt, on standing over sulphuric acid *in vacuo*, becomes anhydrous, and can then be heated to 190° without any change—a characteristic distinguishing it from the sodium compound of aceto-acetic ether. The analysis of the dried salt resulted as follows:

0.3014 gram substance gave 0.1593 gram Na_2SO_4.

	Calculated.	Found.
Na	16.77	16.81

The dried salt was heated with an excess of ethyl iodide for eight hours at 160° in a sealed tube, when, with the exception of some darkening, no reaction seemed to have taken place. The salt remaining was acidified, heated with mercury to remove iodine, and repeatedly extracted with ether, when unchanged tetrinic acid separated upon evaporation. The sodium salt of tetrinic acid thus differs markedly from that of aceto-acetic ether, for that of the latter reacts with ethyl iodide quite readily. In order to prepare the ethyl ether, therefore, I was compelled to resort to the silver salt of the acid,[1] which, contrary to the statement of Demarcay, is tolerably soluble in water, separating therefrom in needles. This on treatment in the usual way with ethyl iodide gave the ether previously described by Cornelius.[2] It is an oil, insoluble in water, and in cold sodium hydrate; soluble in alcohol and ether; boiling at 176°–178° under 50 mm. pressure. On standing over night with potassium hydrate it dissolves completely, and on acidification yields crystals of an acid which has all the appearances and properties of tetrinic acid. The ether therefore differs from the products of the reaction of the alkyl iodides on the metal derivatives of aceto-acetic ether, for in this case the ethyl is evidently attached to oxygen, since it is saponified by alkalies. The analysis of the oil resulted as follows:

0.2574 gram substance gave 0.1665 gram H_2O and 0.5574 gram CO_2.

	Calculated for $C_7H_{10}O_3$.	Found.
C	59.15	59.05
H	7.04	7.19

The crystalline substance resulting from the saponification of this ether gave on analysis the following results:

[1] Wedel, Ann. Chem. (Liebig) **219**, 106, prepared the ether of pentinic acid by saturating a solution of pentinic acid in alcohol with hydrochloric acid and allowing to stand eight days. The result was a very incomplete etherification. Cornelius follows out this method, with very poor results, his analyses showing that the ether was not as pure as the one I obtained from the silver salt. It is possible that my ether differs from that of Cornelius, for he describes his as a crystalline substance, melting at 30°. The boiling-points of the two are the same, and the analysis of my product proves its purity. Cornelius was unable to obtain tetrinic acid by saponifying this ether with alkalies, while mine readily hydrolyses, forming the salt of tetrinic acid.

[2] Moscheles and Cornelius: Ber. d. chem. Ges. **21**, 2603.

0.1296 gram substance gave 0.2529 gram CO_2 and 0.0666 gram H_2O.

	Calculated for Tetrinic acid, $C_8H_4O_3$.	Found.
C	52.63	53.00
H	5.26	5.71

I will introduce one more experiment with tetrinic acid, for it seems to have a bearing on this case. If tetrinic acid be mixed with acetic anhydride in the cold, no reaction takes place. On slight warming, however, the tetrinic acid dissolves, and on distilling off the anhydride and fractioning the remainder, a neutral colorless oil results which under a pressure of 58 mm. was found to boil at 178°-179°. This substance dissolves slowly in aqueous potassium hydrate, with decomposition, for on acidifying tetrinic acid separates. This oil, on treatment with hydroxyl-amine in alcoholic solution, is simply saponified thereby. The analysis resulted as follows:

0.2032 gram substance gave 0.0950 gram H_2O and 0.4044 gram CO_2.

	Calculated for $C_7H_8O_4\left(\begin{matrix}CO.CH_3\\ \vert\\ CH_2.CO:C.CH_3.CO\\ \llcorner\!\!\!-\!\!\!-O\!\!\!-\!\!\!-\!\!\!\lrcorner\end{matrix}\right)$	Found.
C	53.84	54.18
H	5.13	5.19

All of these results seem, in my mind, to show a difference between aceto-acetic ether and tetrinic acid, which can be explained by the assumption that one contains an hydroxyl group while the other does not. The substance which is not reduced by sodium-amalgam, which gives an acetyl derivative with acetic anhydride, the sodium salt of which is so extremely stable—that is, tetrinic acid—could be taken as the one containing the hydroxyl group: the other, easily reduced, yielding with acetyl chloride no acetyl derivative, with a reactive sodium salt, as the one containing the carbonyl group. Why this difference exists in the behavior of two such analogously constituted substances as aceto-acetic ether and tetrinic acid is not so apparent.

The determination of the molecular weight of tetrinic ether by Cornelius[1] seems to leave no doubt that tetrinic acid has the constitution represented by the formula $\begin{matrix}CH_2.COH\\ \vert\\ O\!\!\!-\!\!\!-\!\!\!\lrcorner\end{matrix} : CCH_2.CO$. It is

[1] Ber. d. chem. Ges. 22, 243.

a lactone—an intra-molecular ether, where aceto-acetic ether, $CH_3.CO.CH_2.COOC_2H_5$, is an ordinary inter-molecular one. Apparently the lactone grouping here is more negative than the carbethoxyl in aceto-acetic ether; the oxygen atoms, so to speak, surround the carbonyl group—provided we accept the existence of a carbonyl group in these substances. This would account for the increased stability of the salts, the ability of tetrinic acid to decompose carbonates of the alkalies, and also for the fact that tetrinic acid would more probably contain an hydroxyl group than a carbonyl group. Certain it is that tetrinic acid yields an acetyl derivative where aceto-acetic ether does not; and, just as certainly, aceto-acetic ether is readily reduced while tetrinic acid is not. At the time when Wislicenus wrote the paper referred to above, chemists saw no difficulty whatever in assuming that the sodium atom in the metallic derivatives of such bodies as we have under discussion, could be attached to a carbon atom, for at the time of the publication of the article referred to they became acquainted with the acid nature of the nitro-methanes, and unhesitatingly accepted this disposition of the sodium in the metallic compounds of the latter bodies, as, for example, in sodium nitro-methane, $O_2N.C\lessdot^{H_2}_{Na}$. At the present time, however, many are coming to agree with Michael,[1] who says: "Nach meiner Meinung existirt überhaupt kein Sauerstoffhaltiges Produkt, worin ein Metall direkt an Kohlenstoff gebunden ist, sondern es ist stets mit dem Sauerstoff gebunden."

Of course, such a view necessitates the acceptance of a constitution for aceto-acetic ether differing from that of its sodium derivative, provided the deduction drawn from the behavior of tetrinic acid developed above be correct.

Wislicenus's paper, at the time of its publication, led to an almost universal acceptance of Frankland and Duppa's formula for aceto-acetic ether—$CH_3.CO.CH_2.COOC_2H_5$. Sodium could then, despite its positive nature, be attached to carbon, while in closest proximity we have an oxygen atom, attached to carbon in such a way as as form an unsaturated compound, for the grouping $>C{:}O$ must be considered as unsaturated. Some doubts were raised by a few chemists, notably by Claisen,[2] who published a research on the condensation-products of acetone,[3] and subse-

[1] J. prakt. Chem. [2] **3**, 507. [2] Ann. Chem. (Liebig) **218**, 123. [3] Ibid. **180**, 1.

quently one on the reactions which take place between aldehyde on the one hand, and acetone, aceto-acetic or malonic ether on the other. Claisen showed that when acetone is treated with hydrochloric acid, a condensation-product, mesityl oxide, is produced. In mesityl oxide the methyl group of one acetone molecule loses two hydrogen atoms in conjunction with an oxygen atom of another acetone molecule, producing water and the desired body, thus:

$$CH_3.CO.CH\boxed{H_2 + O}C<\begin{matrix}CH_3\\CH_3\end{matrix}=CH_3.CO.CH:C<\begin{matrix}CH_3\\CH_3\end{matrix}+H_2O.$$

This reaction was subsequently extended so as to include all aldehydes, ketones and ketone-acids which contain a methyl- or methylene group in juxtaposition to the carbonyl- or carboxyl group. All of these bodies can part with the hydrogen of these groups, and this, with the oxygen of another ketone or aldehyde, will form water and leave a condensation-product. Claisen compared the action of aceto-acetic ether toward benzaldehyde with that of acetone.

If we ascribe the ketone formula to aceto-acetic ether, Claisen could see no reason why this substance should not behave exactly as does acetone, toward benzaldehyde. Acetone when condensed with benzaldehyde can form two products—

$$CH_3.CO.CH_3 + HOC.C_6H_5 = CH_3.CO.CH:CH.C_6H_5 + H_2O;$$

and $C_6H_5.CH:CH.CO.CH_3 + HOC.C_6H_5 =$

$$C_6H_5.CH:CH.CO.CH:CH.C_6H_5 + H_2O—$$

while aceto-acetic ether forms but one. For this reason Claisen concluded that the reaction took place as follows:

$$\begin{matrix}H_3C.C.O\boxed{H}\\\|\quad\boxed{+H}\\H_5C_2OOC.C\boxed{H\quad O}\end{matrix}>C.C_6H_5=\begin{matrix}H_3C.C.O\\\|\\H_5C_2OOC.C\end{matrix}>CH.C_6H_5+H_2O;$$

and that aceto-acetic ether is not a true ketone. The ethyl and methyl substituted-aceto-acetic ethers do not react with aldehyde at all unless under great provocation. These reactions would point to a difference in constitution between aceto-acetic ether and acetone, and in considering the subject should certainly be taken as evidence bearing on the case. However, it must be taken into consideration that Claisen's work only extended to the condensation of these aldehydes with aceto-acetic ether; he did not en-

deavor to prove that the substances so produced were not ketones, simply considering the difficulty of reaction with the methyl group as sufficient proof of their constitution. Moreover, he himself showed that[1] diethyl-aceto-acetic ether—where we undoubtedly have the ketone formula—reacts with aldehydes only with great difficulty. It seems to me that these condensation-reactions with aceto-acetic ether and similar substances are not sufficiently understood to enable us to draw conclusions therefrom, and, most certainly, will bear further investigation.

By reason of Claisen's work, and the investigations upon so-called tautomeric compounds, the whole subject was once more brought into prominence, and at that time Baeyer[2] took the field in behalf of the ketone constitution, laying great stress upon the work done by Purdie,[3] on the addition of sodium ethylate to fumaric ether—

$$\begin{array}{l} H_5C_2OOC.CH \\ \| \\ H_5C_2OOC.CH \end{array} + \begin{array}{l} Na \\ | \\ O.C_2H_5 \end{array} = \begin{array}{l} H_5C_2OOC.C\lessgtr{}^{H}_{Na} \\ | \\ H_5C_2OOC.C\lessgtr{}^{O.C_2H_5}_{H} \end{array}.$$

In this reaction sodium is, undoubtedly, primarily attached to carbon, and, as the position of the sodium atom in sodium aceto-acetic ether and in similar ethers has been taken as a criterion of the constitution of these bodies—it being supposed that on substitution of the sodium by some radicle, this radicle would occupy the position vacated by the metal—the fact is of importance that a body can exist in which sodium is attached to carbon, even though oxygen be present in the compound. Baeyer acknowledges that in regard to aceto-acetic ether matters are complicated by the fact that, according to his theory of "Pseudo" forms, the atomic grouping $-CH_2-CO-$ can change, under proper conditions, into $-CH=COH-$ but calls attention to the fact that when acetyl chloride or acetic anhydride reacts with an organic compound containing the arrangement $-CH=CONa-$, an acetyl derivative having the acetyl connected directly with the oxygen, is always formed; while, when the same reagents are brought in contact with aceto-acetic ether, the acetyl group becomes attached to carbon. Hence he thinks we would be safe in saying that sodium aceto-acetic ether has a constitution which does not contain the group $-CH=CONa-$, but $-CO-$

[1] Claisen and Mathews: Ann. Chem. (Liebig) **218**, 170.
[2] Ber. d. chem. Ges. **18**, 3454. [3] J. Chem. Soc. **39**, 344; **47**, 855.

CHNa—. Michael[1] briefly mentions a reaction by which he obtains a neutral oil from the action of chlor-carbonic ether on sodium aceto-acetic ether, in which case he assumes that the group $-COOC_2H_5-$ must be attached to oxygen, as follows:

$$\begin{matrix} H_3C.C.ONa \\ \| \\ H_5C_2OOC.CH \end{matrix} + Cl.COOC_2H_5 = \begin{matrix} H_3C.C.OCOOC_2H_5 \\ \| \\ H_5C_2OOCH \end{matrix} + NaCl.$$

Since then I have shown, as will be seen from the following paper, that the action of chlor-carbonic ether on sodium acetone produces a similar body, as follows:

$$\begin{matrix} H_3C \\ H_3C \end{matrix} > CONa + ClCOOC_2H_5 = \begin{matrix} H_3C \\ H_3C \end{matrix} > COCOOC_2H_5 + NaCl;$$

and a similar discovery, as yet unpublished *in extenso*, was made in Baeyer's laboratory by Zedel,[2] in trying the action of chlor-carbonic ether on sodium acetyl-acetone, the compound

$$\begin{matrix} CH_3.C:CH.CO.CHO \\ | \\ O.COOC_2H_5 \end{matrix}$$

being produced. We thus have three cases in which it seems to be proved that the sodium is not attached to the carbon but to the oxygen, in the sodium derivatives. This being the case, the formation of the ethyl, methyl, acetyl, and similar derivatives of aceto-acetic ether must be explained by assuming the formation of intermediary addition-products, for in all cases (saving that of chlor-carbonic ether) these radicles replacing sodium are undoubtedly attached to carbon.

The reactions, assuming the formation of intermediary addition-products, have been formulated by Michael[3] as follows:

$$CH_3.C(ONa):CH.COOC_2H_5 + C_2H_5I = \begin{matrix} CH_3.CI.CH(C_2H_5).COOC_2H_5 \\ | \\ ONa \end{matrix},$$

and

$$\begin{matrix} CH_3.CI.CH(C_2H_5).COOC_2H_5 = \\ | \\ ONa \end{matrix}$$

$$CH_3.CO.CH(C_2H_5).COOC_2H_5 + NaI,$$

with similar changes assumed for the other substitutions. From these reactions the constitution of the sodium derivatives of aceto-

[1] J. prakt. Chem. [2] **37**, 474.
[2] Alexander B. Smith: Inaugural Dissertation, Munich, 1889.
[3] J. prakt. Chem. [2] **37**, 487 *et sub.*

acetic ether, acetone and similar ketones, seems undoubted—the sodium is attached to oxygen. What is the constitution of the free ketones? The answer is not by any means so easy, for here reactions seem to contradict one another much more. I have already called attention to the difference between tetrinic acid and aceto-acetic ether, which seems to argue in favor of the ketone-constitution of the latter; and to Claisen's researches, which seem to show the other formula to be the correct one. I will simply, therefore, in conclusion call attention to one or two reactions which seem to show a difference between the action of sodium aceto-acetic ether and aceto-acetic ether, and to point towards a difference in their constitution. Sodium ethylate, and even alcohol, can add itself to unsaturated compounds,[1] as Newbury and Chamot have shown. In a research undertaken by Michael and myself, the results of which are as yet unpublished, we show that sodium aceto-acetic ether can add itself to unsaturated ethers, exactly as sodium ethylate does. For instance, we have but to mix sodium aceto-acetic ether in alcoholic solution with cinnamic ether, and allow the whole to stand over night in the cold, when the sodium compound of the addition-product separates as a fine crystalline body.[2] To show the radical difference between sodium aceto-acetic ether and the free oil, I prepared the following experiments: I mixed aceto-acetic ether with cinnamic ether and heated in a metal bath until boiling, with no result. I then heated the mixture with zinc chloride in a sealed tube at 150° with no result; and finally with potassium carbonate at 180° for two days, when, besides the formation of a little dehydracetic acid, no result was observed. Aceto-acetic ether, therefore, does *not* add itself to unsaturated compounds in the manner of sodium aceto-acetic ether.

It occurred to me that acetone would give a sodium derivative similar to that of aceto-acetic ether, and with this end in view I began to experiment on the action of sodium on acetone—as was published in a short preliminary paper in this Journal[3]—and I will embrace this opportunity to give a more detailed account of this reaction. In order best to prepare acetone-sodium for use, small quantities of sodium (from one to two grams) should be finely powdered under boiling toluene, the oil carefully washed away

[1] This Journal **12**, 519.

[2] The details of this research will appear shortly.

[3] This Journal **12**, 355.

with dry ether, and the flask with the sodium and ether connected with an inverted condenser, a dropping-funnel, and an apparatus yielding pure and dry hydrogen. When all of the air has been expelled from the apparatus by means of the hydrogen, acetone, diluted with an equal volume of dry ether, is added through the dropping-funnel, when hydrogen is evolved and a white, flaky precipitate of acetone-sodium is formed. On standing this becomes dark red, but by quickly filtering, drying on a porous plate *in vacuo* over sulphuric acid and paraffin, I was enabled to obtain some analyses the numbers of which were published in the preliminary notice. It was necessary to prove, in the first place, that the gas evolved was hydrogen, and in the second, that the sodium derivative reproduced acetone on addition of dilute acids. In order to prove the first, a small flask was fitted with a dropping-funnel and gas delivery-tube, and then, after placing 0.05 gram sodium therein, the whole apparatus was filled with ligroine and the opening of the delivery-tube connected with a gas measuring-tube. Acetone was then added, and the reaction continued until all of the sodium had disappeared. The ligroine in the gas measuring-tube was then removed by washing with alcohol and water, when the remaining gas was found, in all of the experiments, to be only slightly less than that required for the displacement of one atom of hydrogen by one of sodium in acetone. The gas so obtained was analysed, and proved to be pure hydrogen. The first question is thus settled—sodium reacts with acetone, generating hydrogen. One gram of powdered sodium was placed under anhydrous ether, acetone was added as described previously, the sodium compound formed was quickly filtered, dried on a porous plate and added to water. The slightly-yellow solution was acidified with dilute hydrochloric acid, and extracted repeatedly with ether; the ethereal solution was dried over calcium chloride and the ether distilled, when no residue remained. There is therefore no sodium compound of a condensation-product of acetone contained in the substance. The operation was repeated with one gram of sodium, the sodium compound formed acidified with dilute hydrochloric acid and the solution tested for acetone, without shaking with ether. The tests employed for acetone were (1) the iodoform test, (2) the test with precipitated oxide of mercury. Both of these showed large quantities of acetone to be present. The second question also is therefore answered.

Acetone-sodium regenerates acetone on the addition of acids. The mother-liquors from a number of operations by which acetone-sodium had been prepared, were united, washed with water, dried over calcium chloride and the ether distilled. A small quantity of a dark-colored oil remains, which on fractioning had approximately the odor and boiling-point of mesityl oxide, the quantity being too small, even from a large number of operations, to have its constitution definitely settled, nor, indeed, is that necessary, as the acetone-sodium is the only object of interest. The fact remains that a certain amount of a higher-boiling condensation-product is formed at each operation in the preparation of acetone-sodium. The latter is a white, amorphous substance, which, when exposed to the atmosphere, rapidly decomposes and turns red; it is therefore, as would be expected, considerably less stable than is sodium aceto-acetic ether. When perfectly dry it can be kept apparently unchanged for some time.

The problem which presented itself now was to determine, if possible, the position of the sodium atom in this derivative, and with this end in view Mr. Higley and I studied the action of chlorcarbonic ether on acetone-sodium, the results of which investigation are contained in the following paper. The same questions, of course, arise with regard to the constitution of acetone, as did in regard to that of aceto-acetic ether; yet we would be slow to accept such an unfamiliar formula as $CH_3.COH:CH_2$ for the former substance. Undoubtedly acetone has some of the characteristics of an unsaturated compound, as, for instance, when treated with gaseous hydrochloric acid, the latter is rapidly and completely absorbed; and when acetone and sulphuric acid are brought together, a violent reaction results, with the formation of a compound apparently similar to ethyl- and methyl-sulphuric acids.[1] I hope by an investigation of these substances to throw some further light upon the constitution of acetone. For the present, I believe that we must, in consideration of the difference in behavior of the free ketones from unsaturated compounds, conclude that the old formula containing the carbonyl group should be assigned to them; and that the sodium derivatives prepared from these substances contain the group $-CONa=C-$. In the reactions which I have cited, it will have been observed, however, that a number of changes which the ketones undergo can best be

[1] Kane: Ann. der Phys. Pogg. **24**, 479.

explained by the assumption that they contain the grouping —COH=C—. This chameleon-like behavior of these substances points toward a great instability of either atomic grouping, so that our future investigations will, possibly, show us that these bodies can assume either of the constitutions assigned to them. The sodium derivatives, however, always contain the grouping given above.

In this paper I have not taken into consideration the question of tautomerism in the aromatic series or its derivatives, which has been of late so beautifully elucidated by Nef. I am inclined to think that the considerable differences which exist, even between the di-, tetra-, and hexahydro benzene derivatives and those of the fatty series, often render conclusions drawn in the one inapplicable in the other.

III.—THE ACTION OF CHLOR-CARBONIC ETHER ON ACETONE-SODIUM.

By Paul C. Freer and George O. Higley.

In order to prove the nature of the sodium derivative, and also with a view to ascertaining the position of the sodium atom in the acetone radicle, we performed the experiments, the details of which are given below.—

Finely-powdered sodium is placed in an Erlenmeyer flask and covered with anhydrous ether; the flask is then connected with an inverted condenser, dropping-funnel, and an apparatus yielding pure hydrogen, and, after replacing the air with hydrogen, acetone is slowly added, until all of the sodium has been changed to acetone-sodium. Chlor-carbonic ether is then gradually dropped in, when a most violent reaction results, the ether boiling and the acetone-sodium becoming dark-colored. When the amount of chlor-carbonic ether calculated for the sodium has been added, the whole is allowed to stand for an hour or two, when the reaction with the chlor-carbonic ether will have been entirely finished, chloride of sodium having separated as a white precipitate at the bottom of the flask. It is best to perform this operation with small quantities of sodium, acetone and chlor-carbonic ether—say, 1 gram of sodium, an excess of acetone, and 4.7 grams of chlor-carbonic ether—and to unite the results of about ten reactions in

which these quantities have been used, before attempting to isolate the bodies formed. When a sufficient amount has been prepared, water is added to dissolve the sodium chloride; the ether is separated and washed several times with water, dried over calcium chloride and then evaporated, when a yellow oil remains, of which the major portion, on fractional distillation, boiled between 125° and 135°, while a minor part passed over as the temperature rose to 250°. The high boiling portion contains an oil boiling between 112°–112½°, at 30 mm. pressure, and which will be the subject of a future investigation. The low boiling portion was fractioned several times, after which it distilled at 128°–129°.

The first analysis resulted as follows:

I. 0.1089 gram substance gave 0.1021 gram H_2O and 0.2275 gram CO_2.

II. 0.1685 gram substance gave 0.1462 gram H_2O and 0.3518 gram CO_2.

	Calculated for $C_8H_{10}O_3$.	Found. I.	Found. II.
C	55.40	56.96	56.96
H	7.60	10.20	9.64

Evidently, provided an isomer of aceto-acetic ether had been formed, the oil contained some substance which increased the amount of carbon and hyrogen, and mesityl oxide, with a percentage of 73.46 for the carbon would change the numbers found on analysis, even though present in but small quantities, quite markedly; while its removal by distillation would be impossible, as its boiling-point is 130°. As a consequence of this theory, the oil was treated with phenyl-hydrazine and allowed to stand for a little while, a slight warming taking place on the addition of this reagent. The whole was then driven over with steam, the oil collected in the receiver, shaken out with ether, and then dried over calcium chloride, and the ether evaporated, when the residual oil, on fractioning until apparently pure, was analysed.

I. 0.1371 gram substance gave 0.2775 gram CO_2 and 0.1149 gram H_2O.

II. 0.1226 gram substance gave 0.2499 gram CO_2 and 0.1004 gram H_2O.

	Calculated for $C_8H_{10}O_3$.	Found. I.	Found. II.
C	55.40	55.10	55.73
H	7.60	9.10	9.10

In each case the percentage of hydrogen found has been too high, so that the purity of the substance must be doubted, yet in all probability the impurity boils at exactly the same temperature as does the oil itself, so that it is not to be removed by fractioning. We hope, during next year, when our supply of chlor-carbonic ether will be replenished, to repeat the formation of this body, with the hope of securing more accurate hydrogen determinations. The constitution of the body is, however, abundantly proved by the following experiments.

A determination of the vapor-density of the oil, according to the Victor-Meyer method, gave the following results:

Substance.	*T.*	*V.*	*B.*	*D.* Calculated.	Found.
I. 0.1359 gram.	30°	29.6 cc.	733 mm.	4.50	4.27
II. 0.2040	29	50	733	4.50	4.44

The density of 4.44 calls for a molecular weight of 128.18, while that of aceto-acetic ether is 130, showing conclusively that here we have to deal with a substance of equal molecular weight.

The product of the action of chlor-carbonic ether on sodium-acetone is a colorless oil, insoluble in water, soluble in alcohol and ether in any proportion, possessing a pleasant, fruity odor, and boiling at 128°–129°. It does not react with phenyl-hydrazine, nor does its alcoholic solution give any color-reaction with ferric chloride. On heating in a sealed tube with dilute hydrochloric acid, it is decomposed into carbon dioxide, alcohol, and acetone. There remains a slight odor as of a hydrocarbon, which may possibly indicate the impurity which rendered the analyses inaccurate.

In order more definitely to study the products formed, this decomposition was performed quantitatively. For this purpose an Erlenmeyer flask was fitted with a double-bored stopper, into one of the openings of which was placed a tube connecting with a train of gas wash-bottles containing caustic potash; into the other was placed an inverted condenser, connected by means of a long double-bent tube, with a train of sulphuric-acid wash-bottles, and with the ordinary potash combustion-bulbs; a slow stream of air could be passed through the apparatus by means of an aspirator. A weighed quantity of substance was now placed in the flask with 250 cc. of dilute hydrochloric acid (1 to 20); air was passed through until all carbon dioxide had been expelled from the apparatus; the potash-bulbs were attached, and the liquid then

heated to boiling. In this manner all of the carbon dioxide given off could be collected in the potash-bulbs, while any accidental diffusion backward toward the caustic-potash train was prevented by placing a Bunsen valve at the end of the tube connecting that portion of the apparatus with the Erlenmeyer flask. The determination was made several times, but as the results ran very close together, I will enter but one of them here.

Substance used, 0.4992 gram.

CO_2 found at the end of 9 hours, 0.1152 gram.

15	0.1324
24	0.1472
33	0.1576
42	0.1618
51	0.1665
59	0.1666

	Calculated.	Found.
CO_2	33.84	33.38

This reaction is interesting in several ways, showing as it does the character of such saponifications. In the first nine hours, about 70 per cent. of the ether is decomposed; in fifteen hours, about 79 per cent.; in twenty hours, about 88 per cent.; the reaction continuing with diminishing velocity until at the expiration of fifty-one hours it is complete, the potash-bulbs gaining but 0.0001 gram in the following eight hours. This reaction shows conclusively that the product of the action of chlor-carbonic ether on acetone is saponified by boiling with dilute hydrochloric acid, yielding carbon dioxide. In order to determine the other substances formed, the hydrochloric acid remaining after saponification was partially distilled on a sand-bath, the distillates from several operations united and redistilled, until a moderately concentrated solution of the supposed acetone and alcohol was obtained. A portion of this was treated with acetic acid and sulphuric acid, boiled for a short time in a flask fitted with an inverted condenser, and then distilled, when acetic ether passed over, showing conclusively that alcohol as well as carbon dioxide had been produced. Lastly, the remaining portion was tested for acetone according to two methods: (1) by means of the test with precipitated oxide of mercury; and (2) by means of phenyl-hydrazine acetate; both of which showed acetone to be present. The oil therefore decomposes into carbon dioxide, alcohol, and acetone.

These results may be summed up as follows:

The oil produced by the action of chlor-carbonic ether on acetone-sodium gives figures on analysis, and possesses a vapor-density, which show it to be an isomer of aceto-acetic ether. It does not react with phenyl-hydrazine, nor does it give a color-reaction with ferric chloride, showing a marked difference in properties from aceto-acetic ether. It is decomposed into carbon dioxide, acetone, and alcohol on boiling with dilute acids. All of these reactions seem to show that we have to deal with a body formed as follows:

$$\begin{matrix}CH_3\\CH_2\end{matrix}\!>\!C(O.Na)+Cl.COOC_2H_5=\begin{matrix}CH_3\\CH_2\end{matrix}\!>\!CO.COOC_2H_5+NaCl.$$

The body forms addition-products with bromine, but slowly, but when placed in the sunlight *substitution* takes place rapidly, all of the products formed being of an oily nature, which rendered purification impossible. This indifference toward bromine might be taken as arguing against the formula given above, but then we must consider that, not unfrequently, unsaturated organic compounds, where their nature is extremely negative, do not take up bromine at all—as, for example, in the case of the dicarbon-tetracarbonic ether $\begin{matrix}COOC_2H_5\\COOC_2H_5\end{matrix}\!>\!C=C\!<\!\begin{matrix}COOC_2H_5\\COOC_2H_5\end{matrix}$ of Conrad and Guthzeit.[1]

Another point to which, in fairness, attention should be called is the low boiling-point of the substance, 128°–129°. This should not, however, be taken as counterbalancing the definite proofs of the constitution of the substance given above, as, in the first place, but two or three substances of this class are known, and, in the second, isomers often exhibit very varying boiling-points. There seems indeed no formula, other than the one assigned above, possible for an isomer of aceto-acetic ether synthesised as has been the substance prepared by us. There seems to be no doubt, therefore, that in the case of acetone-sodium the metal is attached to oxygen.

We intend to continue the investigation of this most interesting substance.

[1] Ann. Chem. (Liebig) **214**, 76.

THE PROTEIDS OR ALBUMINOIDS OF THE OAT-KERNEL.[1]

By Thomas B. Osborne.

I.—Historical.

The proteids contained in or derived from the oat-grain have been specially studied by J. P. Norton, Baron von Bibra and Dr. W. Kreusler. Norton[2] recognised three proteids, *viz.* 1. *Albumin* —0.5–2.17 per cent.—which was taken up from the "epidermis" (after starch had been mechanically removed by elutriation with slightly ammoniacal water), by boiling with acetic acid, and was precipitated by neutralising the solution. 2. *Casein* (or *avenine*, as Johnston, in whose laboratory the work was done, named it)—15.76–17.72 per cent.—which was dissolved in the slightly ammoniacal water used in separating starch, and thrown down by acetic acid. 3. *Glutin*—1.33–2.47 per cent.—extracted by alcohol and separated from oil by means of ether, and from sugar by water.

Von Bibra[3] found that no coherent gluten could be got from oat-flour by kneading in water. He recognised *Albumin*—1.24–1.52 per cent.—precipitated by boiling the cold-water-extract of the ground oats; *Casein*—0.15–0.17 per cent.—the body separating from the hot alcohol-extract on cooling; *Plant-gelatin* (Dumas' *glutin*, Taddei's *gliadin*)—3.00–3.25 per cent.—the substance soluble both in hot and cold alcohol; and *Nitrogenous substance insoluble in water and alcohol*—11.38–14.85 per cent.

Kreusler[4] found *Oat-Gliadin* soluble in weak alcohol and *Oat-Legumin* soluble in very dilute alkali.

Since the date of Kreusler's work, 1869, our knowledge of proteid bodies and of the methods for their investigation has been considerably extended. This advance has been chiefly in the study of the animal proteids, but little real progress having been made in our knowledge of the vegetable albuminoids. The following research was undertaken with a view to applying the newer

[1] An abstract of this paper was read by the author before the National Academy of Sciences, in Boston, November 13th, 1890.

[2] Am. J. Sci. [2] **3**, 330 (1845); **5**, 22 (1848).

[3] Die Getreidearten und das Brod (Nürnberg, 1860).

[4] J. prakt. Chem. **107**, 17.

methods of study to the plant-proteids that have agricultural importance.

II.—Oat-proteids extracted by Weak Alcohol.

(*a*) *Kreusler's Work.*

The oat-proteid soluble in weak alcohol was first examined, and, as results differing from Kreusler's were obtained, it will be well to give here a brief summary of his work.

Kreusler found that, on extracting ground oats with alcohol of 80 per cent. and concentrating the extract to one third of its volume, a considerable amount of substance separated which, after subsiding from the solution, became a tough, transparent mass of amber-yellow color. The solution decanted from this substance and further concentrated yielded a second deposit. The liquid poured from this second deposit yielded, on still further concentration, a third. The three sediments were united and dissolved in 80 per cent. alcohol at a gentle heat. On cooling, the greater part of the substance precipitated. After decanting the liquid, this precipitate was treated with absolute alcohol, which caused it to gather on the walls of the vessel as a tenacious mass. After treating with ether and again with absolute alcohol, it was dried over sulphuric acid. This Kreusler designated "A."

By concentrating the solution decanted from A, on cooling, he obtained a second precipitate "B." The filtrate from B by similar treatment yielded a third precipitate "C."

These three precipitates showed the same behavior with various reagents and appeared to differ only in their degree of purity. The reactions agreed with those of gliadin from wheat, which, according to Ritthausen, contains 18 per cent. of nitrogen.

Kreusler found that:

A contained 16.22 per cent. of nitrogen.
B " 16.21 " " "
C " 15.36 " " "

These three preparations were united, dissolved in dilute acetic acid and fractionally precipitated by dilute potash. Thus were obtained three precipitates:

I with 16.00 per cent. of nitrogen.
II " 16.51 " " "
III was too small in amount for analysis.

By this treatment the substance was separated into two portions of different nitrogen-content.

Kreusler in the next place prepared a new extract with alcohol of 80 per cent. from five pounds of ground oats, concentrated the solution until nearly all the alcohol was removed, and on cooling and treating the precipitate with ether and absolute alcohol and drying over sulphuric acid, obtained thirty grams of substance having properties like the former preparations, but not wholly soluble in acetic acid. This precipitate contained 15.36 per cent. of nitrogen. When it was heated with acetic acid, a residue was left, having 14.81 per cent. of nitrogen. The acetic-acid solution by three partial precipitations with dilute potash, gave, as before, precipitates I, II and III—the third being too little for analysis. The composition was:

	I.	II.
Carbon	...	53.41
Hydrogen	...	7.15
Nitrogen	16.99	17.14

This treatment, however, had failed to yield a product having as much nitrogen as Ritthausen's gliadin.

I and II were, therefore, united and dissolved in 60-per cent. alcohol at a gentle heat. The solution was brownish yellow, and on cooling a part of the substance precipitated. The filtrate from this precipitate gave a second precipitate when treated with absolute alcohol. These precipitates were united and called A. The alcoholic filtrate contained a considerable amount of substance which was separated by concentration and gradual precipitation with absolute alcohol. This precipitate was marked B and resembled A in appearance. They contained:

	A.	B.
Carbon	...	52.64
Hydrogen	...	7.66
Nitrogen	17.71	16.70

Since the substance was precipitated in the presence of a considerable amount of acetic acid and might be thought to retain some of the latter, the just-described process was repeated with A, and potash added to perfect neutralisation. The precipitate thus obtained was slightly washed with water, and after dissolving in 60-per cent. alcohol was precipitated with absolute alcohol. B

was dissolved directly in weak, and precipitated by absolute alcohol. These products then had the following composition:

	A.	B.
Carbon	52.94	53.12
Hydrogen	7.71	8.15
Nitrogen	17.28 17.30	17.20

These preparations were next united and dissolved by heating in 60-per cent. alcohol; a varnish-like mass deposited on cooling. This process was repeated several times, and the substance was finally dried with absolute alcohol. It had the following composition, as found in analyses I and II:

	I.	II.	Gliadin. Oats (Kreusler).	Gliadin. Wheat (Ritthausen).
Carbon	52.94	52.59	52.59	52.60
Hydrogen	7.58	7.65	7.65	7.00
Nitrogen	17.71	...	17.71	18.06
Sulphur	1.71	1.61	1.66	.85
Oxygen	20.06	...	20.39	21.49
	100.00		100.00	100.00

The alcoholic solution after concentrating gave on cooling a preparation with 17.2 per cent. nitrogen. Kreusler rejected the highest carbon-determination (obained without the use of lead dioxide) as probably erroneous, and wrote his analysis of *oat-gliadin* beside Ritthausen's analysis of *wheat-gliadin*, as quoted above. Kreusler concludes that oat-gliadin is essentially different from wheat-gliadin, and compares at length the behavior of the two towards reagents. The one point of difference he mentions is that the oat-gliadin dissolves in concentrated hydrochloric acid to a scarcely-colored liquid, while wheat-gliadin gives a blue solution.

It is evident from Kreusler's paper that he expected to find the oat-proteid soluble in alcohol to have the same composition as wheat-gliadin. He finally accepted, as pure, a preparation having 17.71 per cent. of nitrogen, according to a single determination.

It is to be noticed on reviewing his analyses that the treatment to which Kreusler submitted his preparations, while on the whole tending to raise the nitrogen-content, sometimes appears to have had the opposite effect, and the conclusion is not improbable that

the fluctuations in the percentage of nitrogen found by him are partly attributable to the then unknown errors involved in the soda-lime method of analysis—errors which Ritthausen[1] and U. Kreusler[2] in later years fully appreciated and made the subject of special investigation.

III.—Oat-proteids extracted by Weak Alcohol.

(*b*) *The Writer's Work.*

1. *Direct Extraction with Alcohol,—Preparations* 1–8.

As Ritthausen had separated the gliadin, mucedin and fibrin found by him in wheat-gluten, from alcoholic solution by fractional precipitations, the writer judged that if more than one proteid were extracted from oats by alcohol, this fact would be shown by differences in behavior and composition of various fractions of the alcoholic extract. Accordingly four kilos of freshly-ground oats were heated on the water-bath with ten liters of alcohol of 0.915 sp. gr. After boiling for half an hour the extract was strained through cloth, the residue pressed out and the extraction repeated. The extracts were united, allowed to stand over night, decanted from sediment and filtered clear. This solution was concentrated to one-third by distillation. After standing for twenty hours at the temperature of the room, the residue deposited a bulky, yellowish precipitate. About four-fifths of the solution was carefully decanted from this precipitate. The remaining one-fifth could not be filtered until a large amount of strong alcohol had been added, which caused the precipitate to separate. After filtering, the precipitate was treated with absolute alcohol, next with ether, and after removing the ether, with absolute alcohol again, and dried over sulphuric acid. This preparation, "1," then weighed 15.5 grams and, dried at 110° C., contained 13.92 per cent. of nitrogen. The liquid decanted from 1 was still further concentrated to about one-third of *its* volume and cooled. The precipitate which formed "2" was treated with absolute alcohol and ether, and, after drying over sulphuric acid, weighed 10.30 grams. Dried at 110° C., it contained 12.36 per cent. of nitrogen. The filtrate from 2 was concentrated to a thick syrup. On cooling, a deposit formed on the bottom of the dish. The syrup was

[1] Pflüger's Archiv **18**, 236 (1878).
[2] Landw. Vs-St. **24**, 37 (1880); ibid. **31**, 248 (1885).

poured off and this deposit treated successively with strong alcohol, absolute alcohol, ether, and finally with absolute alcohol again. After drying over sulphuric acid, this precipitate, "3," weighed 6.82 grams, and contained, when dried at 110° C., 10.37 per cent. of nitrogen.

The alcoholic liquids obtained by washing preparations **1**, **2** and **3** were found to have dissolved a large amount of proteid; they were, therefore, united and concentrated on the water-bath to small volume, and cooled. The abundant deposit was washed with absolute alcohol, ether, absolute alcohol again, and dried over sulphuric acid. The 14.62 grams thus obtained, "**4**," when dried at 110° C., contained 16.27 per cent. of nitrogen. The filtrate from **4** was still further concentrated, and after cooling and adding a large amount of alcohol, gave a precipitate, "**5**," which, when treated as the others, weighed 4.21 grams and contained 6 per cent. of nitrogen. The filtrate from **5** was highly concentrated and treated with absolute alcohol. The precipitate thus thrown down, "**6**," after treating with absolute alcohol, ether, absolute alcohol again, and drying over sulphuric acid, weighed 17.78 grams and contained 8.61 per cent. of nitrogen.

To sum up: From the alcoholic extract, by concentrating and cooling three times, there resulted three preparations, *viz.*:

1, of 15.5 grams, containing 13.92 per cent. of nitrogen.
2, of 10.30 " " 12.36 " "
3, of 6.82 " " 10.37 " "

From the alcoholic washings of **1**, **2** and **3** by concentration and cooling was obtained preparation

4, of 14.62 grams, containing 16.27 per cent. of nitrogen.

And by further concentration and addition of much strong alcohol,

5, of 4.21 grams, containing 6 per cent. of nitrogen.
6, of 17.78 " " 8.61 " "

The principal impurity recognised in these preparations was sugar, which was abundant in **5** and **6**.

These six preparations were examined separately.

1 was warmed with alcohol of 75 per cent., but was only partly soluble, and owing to its slimy nature, could not be filtered. Three volumes of strong alcohol were added, making the solvent equivalent to 2 liters of about 88-per cent. alcohol. After heating to boiling and cooling, a little substance separated, which was filtered

out, together with the undissolved portion. This precipitate and residue, "**1A**," after treatment with absolute alcohol, ether, etc., as before described, weighed 3.68 grams and contained 14.57 per cent. of nitrogen.

The filtrate from **1A**, concentrated to one-third and cooled, deposited but little substance. Addition of an equal volume of water produced a precipitate. The liquid was poured off and the deposit treated with a large amount of absolute alcohol. The residue, "**1B**," after drying, weighed 3.05 grams, and contained 15.39 per cent. of nitrogen. Water was added to the filtrate from **1B**, but only a trifling precipitate resulted. The aqueous solution was then boiled, the coagulum filtered off, washed with absolute alcohol and dried over sulphuric acid. This preparation, "**1C**," weighed 2.45 grams and contained as follows:

COAGULATED PROTEID.—*Directly extracted from Ground Oats by Weak Alcohol*—**1C**.

Carbon	52.66
Hydrogen	6.89
Nitrogen	16.32
Sulphur, Oxygen, Ash	24.13
	100.00

Carbon and hydrogen.—0.3120 gram, dried at 110° C., gave 0.6025 gram CO_2 = 52.66 per cent. C, and 0.1934 gram H_2O = 6.89 per cent. H.

Nitrogen (by Kjeldahl method).—0.5624 gram, dried at 110° C., gave ammonia = 10.75 cc. HCl (1 cc. HCl = 0.00854 gram N) = 16.32 per cent.

Ash could not be determined for want of material.

Nothing more could be obtained out of the filtrate from **1C**.

2 and **3** were united and treated with 400 cc. of boiling alcohol of 0.9 sp. gr. A part dissolved to a deep-red solution. The residue was extracted again with hot dilute alcohol and treated in the same manner as the other preparations. Thus was obtained 9.05 grams of substance "**2** and **3A**" containing 15.47 per cent. of nitrogen.

This preparation was again treated first with hot water and then with hot alcohol of 0.9 sp. gr., but only a little dissolved and the nitrogen-content was unchanged.

The alcoholic filtrate from **2** and **3A** was further examined, but only 2.3 grams of substance with 7.66 per cent. of nitrogen, were obtained. The long heating in very weak alcohol to which preparations **2** and **3** had been subjected, had rendered a large share of the proteid insoluble, and it was therefore lost for further purification.

4 was treated with 500 cc. of alcohol of 0.9 sp. gr., in which a part was insoluble, "**4A.**" This was washed with alcohol and ether, dehydrated with absolute alcohol, and, after drying over sulphuric acid, weighed 8.9 grams. Its analysis follows:

COAGULATED PROTEID.—*Directly extracted from Ground Oats by Weak Alcohol*—**4A.**

Carbon	53.09
Hydrogen	6.96
Nitrogen	16.56
Sulphur } Oxygen }	23.39
	100.00
Ash	.35

Ash.—0.5069 gram air-dried (= 0.4555 dried at 110° C.) gave 0.0016 gram ash = .35 per cent.

Carbon and hydrogen.—0.4354 gram, dried at 110° C., gave 0.8445 gram CO_2 = 52.90 per cent. C, and 0.2716 gram H_2O = 6.91 per cent. H.

Nitrogen (by Dumas' method).—0.5425 gram, dried at 110° C., gave 76.12 cc. gas at 9° C. (barometer 756.3 mm. at 9° C.) = 16.76 per cent., less correction of .20 = 16.56 per cent. N.

The alcoholic filtrate from **4A** was concentrated to small volume, but as a slimy precipitate appeared, which could not be filtered, the solution was mixed with water. This did not cause the substance to separate in a manageable form, so the liquid was boiled, and after cooling the substance deposited as a gelatinous lump. After filtering, the deposit, "**4B**," was treated with absolute alcohol and with ether and dried over sulphuric acid. It weighed 2.6 grams. Its analysis is subjoined:

COAGULATED PROTEID.—*Directly extracted from Ground Oats by Weak Alcohol*—**4B.**

	I.	II.
Carbon	53.12	...
Hydrogen	6.91	...
Nitrogen	16.52	16.39
Sulphur, Oxygen, Ash	23.45	...
	100.00	

Ash.—Very little. Not determined for want of substance.

Carbon and hydrogen.—0.3445 gram, dried at 110° C., gave 0.6700 gram CO_2 = 53.12 per cent. C, and 0.2143 gram H_2O = 6.91 per cent. H.

Nitrogen, I (by Dumas' method).—0.2693 gram, dried at 110° C., gave 37.93 cc. gas at 8° C., less correction of .7 cc. (barometer 756.3 mm. at 9° C.) = 16.52 per cent. N.

Nitrogen, II (by Kjeldahl method).—0.2693 gram substance, dried at 110° C., gave ammonia = 9.68 cc. HCl (1 cc. HCl = 0.00854 gram N) = 16.39 per cent.

The filtrate from **4B** was evaporated to dryness and yielded one gram of substance containing 7.5 per cent. of nitrogen.

6 evidently contained a large amount of sugar. It was first treated repeatedly with water, in which it formed a pasty lump. This was dehydrated with absolute alcohol, and when dried over sulphuric acid weighed 7.63 grams and contained 14.61 per cent. of nitrogen = "**6A.**"

6A was then treated with 100 cc. of water, with which it formed a stringy lump which, after having been thoroughly kneaded under water, assumed a semi-liquid condition and could not be separated from the solution either by boiling or freezing. The solution after concentrating on the water-bath to about 30 cc. was poured into 300 cc. of absolute alcohol. This threw down a curdy white precipitate which, after treating with absolute alcohol and drying over sulphuric acid, weighed 6 grams, and contained 15.67 per cent. of nitrogen when dried at 110° C. = "**6A1.**"

6A1 was treated with 500 cc. of alcohol of 0.9 sp. gr. But little dissolved and the solution was too slimy to filter. The

whole was then concentrated to one-third and cooled, but no separation took place which would allow of filtering or decanting the solution. The solution was, therefore, diluted with water and boiled. After cooling, a curdy precipitate settled out, leaving a turbid liquid. This liquid was decanted and poured into a large amount of absolute alcohol. On standing, a precipitate separated which, when treated with absolute alcohol and dried over sulphuric acid, weighed 0.455 gram and contained, when dried at 110° C., 16.40 per cent. of nitrogen = "**6A2**."

There was thus obtained of the proteid soluble in alcohol a large number of fractional precipitations with different nitrogen-content. It will be noticed, however, that five of these preparations have from 16.27 to 16.56 per cent. of nitrogen. No preparations were obtained having a higher percentage of nitrogen, and none of the other preparations approximate to a constant nitrogen-content.

4 had 16.27 per cent. of nitrogen. When this was separated into two parts, one soluble in dilute alcohol—**4B**— and the other insoluble—**4A**—the two parts were found to contain the same proportion of nitrogen, and exactly agreed in content of carbon and hydrogen. This is what might be expected of a pure proteid, for some of these bodies become insoluble without change of composition, so far as can be detected by our methods of analysis. **1C**, without correction for ash, has nearly the same composition as **4A** and **4B**: a correction would tend to bring it into closer agreement. The amount of substance, however, was insufficient for an ash-determination.

As all the preparations analysed thus far were the insoluble modification of the proteid, a new extract was prepared. Five pounds of freshly-ground oats were boiled up with ten liters of alcohol of 0.915 sp. gr. The extract was pressed out, and added to another five pounds of oats and again heated to boiling. After filtering, a perfectly clear, deep ruby-red solution was obtained. This was concentrated by distillation on the water-bath to about one-third of its original volume. On cooling, a large amount of substance separated. This was thrown upon a filter and, after twenty-four hours, about seven-eighths of the solution had passed through. The filter, with its contents, was then boiled in ten liters of 60-per cent. alcohol, in a flask fitted with a reflux-condenser, for four hours. The substance entirely dissolved to a

clear, deep-red solution. The solution was then concentrated by distillation to about one-half, and cooled rapidly to 35° C., when it filtered readily. The precipitate formed a tough, jelly-like mass which did not adhere to the paper. It was boiled, as before, for several hours, with ten liters of 60-per cent. alcohol until completely dissolved. The perfectly clear solution was concentrated to one-half its volume, during which operation a large part of the substance deposited on the interior of the flask as a thick leather-like coating. This coating readily separated from the glass in large pieces of a dark-brown color. On cooling the liquid, a finely-divided yellowish precipitate appeared which did not settle out on standing. The muddy liquid was poured off and the leathery deposit was minced and treated with absolute alcohol, in order, if possible, to dehydrate the substance and render it pulverisable for analysis, but as it remained forty-eight hours without change, the attempt was abandoned. The substance suspended in the muddy liquid was now caused to separate by adding alcohol. After filtering, washing first with strong, then with absolute alcohol, the precipitate was united to the portion which had been digested with absolute alcohol, and the whole then boiled in two liters of 60-per cent. alcohol in a flask fitted with a return-condenser. After three hours' boiling, about one-half had dissolved. Two liters more of 60-per cent. alcohol were then added and the boiling continued. Considerable proteid still remained in a gelatinous form on the sides of the flask. The solution was filtered off and 1200 cc. of absolute alcohol were poured on the residual substance. This caused the jelly to break up into coarse lumps, whereupon 800 cc. of water were added, making two liters of 60-per cent. alcohol, and the boiling on the water-bath was continued for several hours. Some of the substance dissolved, the liquid was filtered, and the insoluble residue was treated for many days with absolute alcohol. It was then ground to a fine powder while still moist with alcohol, extracted with ether, and dried over sulphuric acid. This preparation, "**7**," weighed 9.1 grams.

The alcoholic solution filtered from the insoluble portion was concentrated to one-half and filtered, while hot, from the large amount of substance which had separated. The latter resembled raw rubber in appearance and consistence, but not in elasticity. It was finely minced, and, after having been digested with absolute alcohol, was pulverised, treated again with absolute alcohol,

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washed with ether, and dried over sulphuric acid. This, "**8**," weighed 26 grams, and was a light powder of yellowish color. Unlike all the other preparations extracted from the oats by weak alcohol, which were analysed, **8** was still largely "uncoagulated" and soluble in that reagent.

These two preparations were analysed with the following results:

COAGULATED PROTEID.—*Directly extracted from Ground Oats by Weak Alcohol*—**7**.

	I.	II.	III.	I. Ash-free.
Carbon	52.98	...	...	53.10
Hydrogen	6.86	...	...	6.87
Nitrogen	16.34	16.41	16.39	16.39
Sulphur, Oxygen,	...	...	...	23.64
Ash	.25	...	...	...
				100.00

Ash.—1.007 grams air-dried substance (=0.9291 gram dried at 110° C.) gave 0.0023 gram ash = 0.25 per cent.

Carbon and hydrogen.—0.5076 gram, dried at 110° C., gave 0.9860 gram CO_2 = 52.98 per cent. C, and 0.3131 gram H_2O = 6.86 per cent. H.

Nitrogen, I (Dumas' method).—0.5000 gram air-dried (= 0.4606 gram dried at 110° C.) gave 64.1 cc. gas at 8° C. (barometer 750 mm. at 15° C.) = 16.54 per cent., less .20 found in blank = 16.34 per cent. N.

Nitrogen, II (Kjeldahl method).—0.5000 gram air-dried (= 0.4606 gram dried at 110° C.) gave ammonia = 8.85 cc. HCl (1 cc. HCl = .00854 N) = 16.41 per cent.

III.—0.5000 gram air-dried (=0.4611 gram dried at 110° C.) gave ammonia = 8.85 cc. HCl = 16.39 per cent. N.

SOLUBLE PROTEID.—*Directly extracted from Ground Oats by Weak Alcohol*—**8**.

	I.	II.	III.	IV.	1. Ash-free.
Carbon	52.92	...	...	...	53.06
Hydrogen	6.93	...	...	...	6.94
Nitrogen	16.33	16.33	16.45	16.54	16.38
Sulphur	2.25	2.21	...	...	2.26
Oxygen	...	...	...	...	21.36
Ash	.24	...	...	...	...
					100.00

Ash.—1.0045 grams air-dried (=0.9027 gram dried at 110° C.) gave 0.0022 gram ash = 0.24 per cent.

Carbon and hydrogen.—0.4821 gram, dried at 110° C., gave 0.9356 gram CO_2 = 52.92 per cent. C, and 0.3003 gram H_2O = 6.93 per cent. H.

Nitrogen, I (Dumas' method).—0.5000 gram air-dried (= 0.4554 gram dried at 110° C.) gave 63.1 cc. gas at 10° C. (barometer 759.5 mm. at 16° C.) = 16.53 per cent., less correction .20 = 16.33 per cent. N.

II.—0.5000 gram (=0.4490 gram dried at 110° C.) gave 62.42 cc. gas at 14° C. (barometer 770.3 mm. at 17° C.) = 16.53 per cent. N.; corrected = 16.33 per cent. N.

III. (Kjeldahl method).—0.5000 gram (=0.4490 gram dried at 110° C.) gave ammonia = 8.65 cc. HCl (1 cc. HCl = .00854 gram N) = 16.45 per cent. N.

IV.—0.5000 gram (=0.4490 gram dried at 110° C.) gave ammonia = 8.70 cc. HCl = 16.54 per cent. N.

Sulphur, I.—1.00 gram air-dried (=0.9107 gram dried at 110° C.) gave 0.1850 gram $BaSO_4$, which, when fused with Na_2CO_3 and reprecipitated, gave 0.1495 gram $BaSO_4$ = 0.020532 gram S = 2.25 per cent.

II.—1.00 gram (=0.9107 gram dried at 110° C.) gave 0.1575 gram $BaSO_4$, which, when fused with Na_2CO_3 and reprecipitated, gave 0.1469 gram $BaSO_4$ = 0.020175 gram S = 2.21 per cent.

These analyses are observed to agree closely with each other, as well as with several of the preparations obtained under various conditions from the first extract already described, as is shown by the following table:—

OAT-PROTEID EXTRACTED BY WEAK ALCOHOL.

	Soluble.	Coagulated					
	8.	**7.**	**1C.**[1]	**4A.**	**4B.**[1]	**4.**	**6A2.**[1]
Carbon	53.06	53.10	52.66	53.09	53.12	...	...
Hydrogen	6.94	6.87	6.89	6.96	6.91	...	...
Nitrogen	16.38	16.39	16.32	16.56	16.52	16.27	16.40
Sulphur	2.26	23.64	24.13	23.39	23.45	...	...
Oxygen	21.36						
	100.00	100.00	100.00	100.00	100.00		

[1] Not corrected for ash.

The figures given by Kreusler for the nitrogen of two precipitates from his first alcoholic extract are likewise in close agreement with the above, *viz.* 16.22 and 16.21 per cent. From his "oat-legumin" Kreusler also extracted by means of alcohol a substance with 16.38 per cent. nitrogen.

It seems hardly probable that such concordant analyses could result from impure preparations or from a mixture of two or more proteids, especially in view of the varying conditions under which the preparations were obtained.

The very high content of sulphur is remarkable. No other analysis of a vegetable proteid approaches this amount. Ritthausen[1] found, indeed, in a single preparation from sesame press-cake 2.36 per cent., but he attributed this high percentage to some foreign substance precipitated with the proteid. He afterwards[2] stated the percentage of sulphur as 1.25, and ascribed the high figure first obtained to calcium sulphate. Among the animal-proteids besides *Keratin*, some forms of human *serum-albumin* contain 2.3 per cent. of sulphur.[3]

The fact that sulphur in my analyses is 0.60 per cent. more than found by Kreusler in his gliadin, indicates that his substance had undergone chemical change during the processes of preparation.

Ritthausen believes to have obtained from wheat-gluten by extracting with alcohol three distinct proteids, to which he applies the names *fibrin*, *gliadin*, and *mucedin*, and he includes under one or the other of these terms all the proteids soluble in alcohol which he and Kreusler found in their extended study of the cereals. That portion of wheat-gluten which is insoluble in alcohol Ritthausen denominated *gluten-casein*.

On the authority of Ritthausen, his names and the composition attributed by him to these substances have passed into chemical literature, and have superseded the various designations and analyses of the older investigators.

The proteid of the oat which I have obtained, soluble in alcohol, differs essentially, however, in composition from all these preparations of Ritthausen and Kreusler. Kreusler's analysis of mucedin from barley-grits alone fairly agrees with my results as respects carbon, hydrogen and nitrogen, but the same chemist's analysis of mucedin from barley-meal gives 0.84 per cent. higher nitrogen than that from grits, and but 0.68 per cent. sulphur.

[1] Pflüger's Archiv **21**, 95 (1880). [2] J. prakt. Chem. **36**, 444.
[3] Starke: Jsb. thier. Chem. **11**, 19.

In case of the other substances the discrepancies are still more decided. The properties and reactions given by Kreusler for the substance called by him *oat-gliadin* are true of the body just described, but these reactions mostly belong to proteids in general, or to the mucedin and fibrin of Ritthausen, and are not characteristic of any one body. Ritthausen states that on evaporating the alcohol solution of the gluten-fibrin prepared by him from wheat-gluten, a pellicle forms on the surface which renews itself as often as removed, and that neither mucedin nor gliadin shows this property. I have frequently observed the formation of films on evaporating solutions of the alcohol-soluble proteid from oats. This body, however, cannot be a mixture of Ritthausen's fibrin and gliadin, as its sulphur-content so largely exceeds theirs.

2. *Extraction with Alcohol after treatment with Water,—Preparation* 9.

Five pounds of oats were treated with water as long as any proteid was dissolved. The residue was then twice extracted with alcohol and strongly pressed. The first alcoholic extract was evaporated so far as to remove nearly all the alcohol. On cooling, the solution became turbid, and after standing deposited a brown, slimy substance exceedingly soluble in dilute alcohol. The liquid was decanted and the precipitate dissolved in dilute alcohol. After evaporating off the alcohol and cooling, the substance separated as before; the aqueous solution was decanted and the slimy residue treated with ether, which extracted a fatty oil from this material and caused it to assume a more solid consistence. The substance was then treated with alcohol of 93 per cent., which dissolved a little and converted the remainder into a solid lump, so that it could be transferred to a flask and digested with ether. By the continued action of ether the viscid substance was transformed into a loose, yellowish powder. After standing under ether for twenty-four hours, the body was filtered out and dissolved in dilute alcohol. This alcoholic solution was filtered and evaporated on the water-bath to a small volume. After cooling, the solution was poured from the gummy substance adhering to the dish, which was washed with water and repeatedly digested with absolute alcohol. As long as the substance retained water, a little dissolved during treatment with alcohol. The residue became granular and brittle, and was easily reduced to a fine

powder. When impregnated with absolute alcohol, the mass rapidly absorbed moisture from the air and became soft and viscid.

After thorough dehydration with absolute alcohol, the substance was rapidly filtered out and dried over sulphuric acid. It weighed 7.88 grams.

In testing the purity of this substance it was found to yield something to water. The whole preparation was, therefore, washed out completely with distilled water, and again treated with absolute alcohol and ether and dried over sulphuric acid. Analysis of this preparation, "9," gave the following results:

SOLUBLE PROTEID—*Extracted by Weak Alcohol from Ground Oats after treating them with Water*—9.

	I.	II.
Carbon	53.64	...
Hydrogen	6.88	...
Nitrogen	15.70	15.36
Sulphur	1.75	...
Oxygen	22.03	...
	100.00	

Ash.—0.6007 gram air-dried left no ash.

Carbon and hydrogen.—0.5886 gram, dried at 110° C., gave 1.1579 grams CO_2 = 53.64 per cent. C, and 0.3642 gram H_2O = 6.88 per cent. H.

Nitrogen, I (Dumas' method).—0.5000 gram air-dried (= 0.4479 gram dried at 110° C.) gave 60.68 cc. gas at 8° C. (barometer 757 mm. at 12° C.) = 15.90 per cent. N, less .20 for blank = 15.70 per cent.

II (Kjeldahl method).—0.5000 gram air-dried (= 0.4479 gram dried at 110° C.) gave ammonia = 8.05 cc. HCl (1 cc. HCl = 0.00854 gram N) = 15.36 per cent.

Sulphur.—0.8958 gram, dried at 110° C., gave 0.1142 gram $BaSO_4$ = 0.0157 gram = 1.75 per cent. S.

3. *Extraction with Alcohol after treatment with Salt Solution—Preparations* **10** *and* **11.**

Five pounds of oats were repeatedly treated with 10 per cent. solution of sodium chloride until nothing more was dissolved, and after pressing out as thoroughly as possible the residue was twice

treated with alcohol of 0.912 specific gravity, being pressed out each time, and the extracts kept separate. The first and second alcohol-extracts were united, evaporated on the water-bath until all alcohol had escaped, and the residue then cooled to 10° C. At this temperature the deposit formed brittle lumps which, after decanting the solution, were treated with ether and absolute alcohol. The lumps were thus brought into a granular state, in which condition the substance was treated for some time with ether until all fat had been removed. It was then dissolved in hot dilute alcohol, filtered and evaporated on the water-bath to a small volume. On cooling the proteid separated in a mass on the bottom of the dish. The aqueous liquid was poured off, and the residue treated with absolute alcohol and ether, whereupon it became brittle and was easily ground to a fine powder. This powder was washed with water until it no longer gave with silver nitrate a reaction for chlorine. It was then treated with absolute alcohol and dried over sulphuric acid. In appearance and behavior it resembled in all respects the substance extracted by alcohol after the oats had been treated with water. When analysed it was found to have the composition stated under "**10.**"

The third alcoholic extract of the oats was treated in the same way, and the product obtained analysed with the following results, "**11**":

SOLUBLE PROTEID—*Extracted by Weak Alcohol from Ground Oats after treating them with Salt-solution*—**10** *and* **11**.

	10.			**11.**	
	I.	II.	III.	I.	II.
Carbon	53.97	...	...	53.55	...
Hydrogen	7.14	...	...	6.80	...
Nitrogen	15.71	15.66	15.68	15.61	15.52
Sulphur	1.80	...	...	} 24.04	...
Oxygen	21.38	...	...		
	100.00			100.00	
Ash	0.56			0.25	

Details of Analyses of **10**.

Ash.—1 gram air-dried (= 0.9361 gram dried at 110° C.) gave 0.0053 gram ash = 0.56 per cent.

Carbon and hydrogen.—0.3443 gram, dried at 110° C., gave 0.6780 gram CO_2 = 53.70 per cent. C, and 0.2200 gram H_2O = 7.09 per cent. H.

Nitrogen, I (Dumas' method).—0.5000 gram air-dried (= 0.4681 gram dried at 110° C.) gave 60.47 cc. gas at 8° C. (barometer 772 mm. at 8° C.) = 15.80 per cent., less .20 for blank = 15.60 per cent. N.

II (Kjeldahl method).—0.5000 gram air-dried (= 0.4681 gram dried at 110° C.) gave ammonia = 8.53 cc. HCl (1 cc. HCl = 0.00854 gram N) = 15.57 per cent. N.

III.—0.5000 gram gave ammonia = 8.55 cc. HCl = 15.59 per cent. N.

Sulphur.—1 gram air-dried substance (= 0.9361 gram at 110° C.) gave 0.1232 gram $BaSO_4$ = 0.0169 gram = 1.80 per cent.

Details of Analyses of **11.**

Ash.—0.8680 gram, dried at 110° C., gave 0.0022 gram ash = 0.25 per cent.

Carbon and hydrogen.—0.3676 gram, dried at 110° C., gave 0.7190 gram CO_2 = 53.42 per cent. C, and 0.2242 gram H_2O = 6.78 per cent. H.

Nitrogen, I (Kjeldahl method).—0.5000 gram (= 0.4715 gram dried at 110° C.) gave ammonia = 8.60 cc. HCl (1 cc. HCl = 0.00854 gram N) = 15.59 per cent N.

II.—0.5000 gram (= 0.4715 gram dried at 110° C.) gave ammonia = 8.55 cc. HCl = 15.49 per cent. N.

4. *Extraction with Alcohol after treatment with Water and Salt-solution,—Preparation* **12.**

Five pounds of oats were extracted with water, and then with 10 per cent. salt-solution as long as anything was removed. The residue was twice digested with alcohol of 0.9 sp. gr., the two alcohol extracts were united and concentrated to a small volume on the water-bath. After cooling, the substance which deposited was filtered out and dissolved in dilute alcohol. The filtered solution was evaporated until nearly all the alcohol was expelled, and finally poured into cold water. The abundant precipitate thus produced settled rapidly, forming a pasty mass on the bottom of the dish, from which the water could be completely

decanted. By treatment with ether and absolute alcohol the substance was rendered dry and brittle, and was easily ground to a yellowish powder. This was transferred to a flask and digested for twenty-four hours with a mixture of absolute alcohol and ether, then washed with ether to remove the alcohol, and dried in the air. The product weighed 12 grams. After dissolving this preparation in dilute alcohol and evaporating to a small volume on the water-bath, the concentrated solution was poured into a liter of cold distilled water. The substance thus precipitated was washed by decantation with distilled water until all chlorides had been removed, then treated with absolute alcohol and ether and dried over sulphuric acid. This preparation was found to have the following composition:

SOLUBLE PROTEID—*Extracted by Weak Alcohol from Ground Oats after treating them with Water and with Salt-solution*—"**12.**"

	I.	II.
Carbon	53.63	...
Hydrogen	7.16	...
Nitrogen	15.83	15.86
Sulphur	1.74	...
Oxygen	21.64	...
	100.00	
Ash,	0.11	

Ash.—0.7593 gram, dried at 110° C., gave 0.0008 gram ash = 0.11 per cent.

Carbon and hydrogen.—0.2850 gram, dried at 110° C., gave 0.5595 gram CO_2 = 53.58 per cent. C, and 0.1836 gram H_2O = 7.15 per cent. H.

Nitrogen, I (Dumas' method).—0.4168 gram, dried at 110° C., gave 56.95 cc. N at 18° C. (barometer 764.5 mm. at 22° C.) = 15.81 per cent.

II (Kjeldahl method).—1.0183 grams, dried at 110° C., gave ammonia = 19.63 cc. HCl (1 cc. HCl = 0.00822 gram N) = 15.84 per cent.

Sulphur.—0.9682 gram, dried at 110° C., gave 0.1218 gram $BaSO_4$ = 0.01673 gram S = 1.74 per cent.

Recapitulation.

The following statement brings together the analyses of the four preparations last described.

PROTEID EXTRACTED FROM OATS BY WEAK ALCOHOL.

After treatment of the meal with—

	Water.	Salt-solution.		Water and Salt-sol.	
	9.	10.	11.	12.	Average.
Carbon	53.64	53.97	53.55	53.63	53.70
Hydrogen	6.88	7.14	6.80	7.16	7.00
Nitrogen	15.70	15.71	15.61	15.83	15.71
Sulphur	1.75	1.80	} 24.04	1.74	1.76
Oxygen	22.03	21.38	}	21.64	21.83
	100.00	100.00	100.00	100.00	100.00

When the above analyses are compared, as below, with those of the preparations obtained without previous treatment of the oats with water or salt-solution, it is evident that we have in hand two quite different and distinct substances, neither of which agrees in composition with Kreusler's *Oat-Gliadin.*

PROTEID EXTRACTED FROM OATS BY WEAK ALCOHOL.

	Without Action of Water or Salt-solution.	After Action of Water or Salt-solution.
	8.	Average.
Carbon	53.06	53.70
Hydrogen	6.94	7.00
Nitrogen	16.38	15.71
Sulphur	2.26	1.76
Oxygen	21.36	21.83
	100.00	100.00

The differences in behavior of the two substances are much more marked than those of composition. The body extracted by alcohol without the previous treatment with water, becomes insoluble in alcohol with great readiness, and, after having been dissolved and precipitated a few times, is again dissolved very slowly and only in a large amount of hot alcohol of 0.9 sp. gr. When wet with absolute alcohol it can be exposed to moist air without becoming gummy.

On the other hand, the body extracted by alcohol after the action of water or 10-per cent. salt-solution shows no tendency to

become insoluble, even after long heating with very dilute alcohol. It is freely soluble even in cold alcohol of 0.9 specific gravity, and, when wet with absolute alcohol, immediately attracts moisture from the air, becoming sticky and viscid. In appearance the two bodies do not materially differ, both being light, yellowish powders, when prepared as described.

Both these substances are soluble in dilute acids and alkalies to solutions from which on neutralisation they precipitate, retaining their solubility in dilute alcohol.

The fact that weak alcohol acts as a solvent for these bodies, which are insoluble in either pure (absolute) alcohol or pure water, is doubtless due to the formation of hydrates that, while insoluble in water, are soluble in alcohol, but that cannot exist in strong alcohol, being thereby dehydrated.

The proteid whose composition is expressed by analysis **8** was first obtained by Norton, who extracted ground oats directly with hot alcohol, distilled the solution carefully to dryness, dissolved out the oil by ether and the salts and sugar by water. Norton designated this body *Glutin*, and considered it "analogous to the glutin of wheat"; he states that the preparation which he thus separated and weighed was no longer soluble in alcohol, but he did not attempt any further investigation of its properties or composition.[1]

Von Bibra, who found in oats 3 per cent. of *Plant-gelatin* (Pflanzenleim), does not describe its mode of preparation, but states that it contained 15.6 per cent. of nitrogen.

Kreusler indeed extracted crushed oats directly by 80 per cent. alcohol, and in his first preparations found 16.22 and 16.21 per cent. of nitrogen; but the substance, from whose analysis he decided upon the composition of *Oat-gliadin*, had been "purified" by dissolving in acetic acid and precipitating by potash solution, and, according to his results, contained 1.3 per cent. more nitrogen, 0.65 per cent. more hydrogen, and 0.6 per cent. less sulphur than exist in either of the proteids soluble in alcohol which I have analysed.

It would be premature to attempt a revision of the nomenclature of these proteids until after re-investigation of the proteids soluble in alcohol derived from the other cereals.

(*To be concluded.*)

[1] Am. J. Sci. [2] **3**, 229.

Contributions from the Chemical Laboratory of Purdue University.

V.—A NEW SOURCE FOR XYLOSE.

By W. E. Stone and Dumont Lotz.

One of us, in applying the furfurol test to a variety of vegetable materials, in search of the pentose carbohydrates, or *pentans*, found that the "cobs" of Indian corn were especially rich in these bodies.[1]

In the preliminary test cited, by distilling the air-dried material with sulphuric acid of 1.254 specific gravity, and precipitating the furfurol thus obtained as furfuramide, the equivalent of twelve to thirteen per cent. of furfurol was obtained. This result, which quite equals that obtained under similar conditions from cherry gum and gum tragacanth, indicated that the corn "cobs" might compare favorably with the latter materials as a source of one or the other of the pentoses. Since the tests mentioned we have repeated the furfurol determinations, making use of a method proposed by Tollens and Chalmot, and privately communicated to one of us. By this method the material is distilled with hydrochloric acid of 1.06 specific gravity, the furfurol thus obtained is precipitated from acetic-acid solution with phenyl-hydrazine, dried in a current of dry air at 60°, and weighed as phenyl-furfurazide. In this way somewhat higher results were obtained. One distillation of the air-dried material gave 21.89 per cent. furfurol, and a second, 22.36 per cent.

Our method of procedure was to extract the pentose carbohydrates from the material by means of strong alkalies, and then by hydrolysis convert them into the specific pentose.

Two and one-half kilos. of finely-ground air-dried "cobs" were digested, cold, with twelve liters of one-per cent. ammonia solution during about thirty hours, for the purpose of removing coloring matters. When drawn off the liquid was of a dark-brown color, but nothing was precipitated from it when several volumes of strong alcohol were added, showing that none of the gummy pentose carbohydrates had been extracted.

The residue, which was perceptibly lighter in color than before this treatment, was next subjected to the action of a sodium hydroxide solution in order to effect solution of the gums. In

[1] This Journal **13**, 73.

his treatment of sugar-beet chips for the extraction of the so-called metapectic acid from which arabinose was first prepared, Scheibler used for this purpose quicklime.[1] Later, one of us by the same process obtained from the fermented residue of malt a gum which, upon hydrolysis, yielded both arabinose and xylose.[2]

Tollens and Allen have found, however, that caustic alkalies gave better results in the preparation of xylose from wheat-straw.[3]

Accordingly, the residue left after extraction with ammonia received enough of a two-per cent. sodium hydroxide solution to cover it, and the whole was boiled during eight hours, the liquor becoming very dark-colored and mucilaginous. After standing eight hours longer the liquid was separated from the residue of fibre and insoluble matter by means of a press. Upon addition of two volumes of 95-per cent. alcohol to this liquor, a voluminous, dark-brown, gummy precipitate was thrown down. This was several times washed with alcohol by decantation. Finally it was redissolved in a little water to which some hydrochloric acid had been added, and then reprecipitated with alcohol. This treatment was repeated several times. The final result was an amorphous substance of light-brown color, which upon exposure to the air seemed slightly hygroscopic, and rapidly blackened. After drying over sulphuric acid this product weighed about 200 grams, or about eight per cent. of the material employed.

A small quantity of this gum was repeatedly dissolved in water and reprecipitated from an acid solution by means of alcohol, with the object of obtaining a pure ash-free product for further study. The last traces of ash were, however, very difficult to remove, and after some months the preparation still contained 0.76 per cent. Spectroscopic examination showed this ash to consist of sodium salts. Two portions of this gum yielded on distillation, respectively, 48 and 50 per cent. of furfurol. This partially-purified material was noteworthy for its solubility in water and its rapid discoloration on exposure to the air. The greater portion of the 200 grams of gum was heated in a flask with two liters of two-per cent. sulphuric acid for twelve hours, an inverted condenser being used to prevent concentration of the acid by evaporation. At the end of this time about 50 grams of amorphous, insoluble matter remained in the flask. The acid liquor was filtered from this

[1] Ber. d. chem. Ges. **1**, 58, 108. [2] Ann. Chem. (Liebig) **249**, 243.
[3] Ibid. **260**, 289.

residue, neutralised with calcium carbonate, and evaporated to a thick syrup. Upon adding about three volumes of strong alcohol to this and boiling, a dark-brown, tasteless gum was precipitated and removed, and the liquid after concentration yielded slowly a mass of dark-colored crystals.

After repeated washings and recrystallisations, two successive portions of crystals were obtained, which were nearly white, sweet to the taste, and reduced Fehling's solution strongly. In all about six grams of this product were obtained, or nearly three per cent. of the 200 grams of gum used. Probably an equal amount of sugar remained in the dark-colored and non-crystallisable mother-liquors. The amount of this product obtained was disappointingly small in view of the promising preliminary indications. The syrups obtained after hydrolysis, however, contained much unchanged gummy matter, and crystallised only slowly and with great difficulty. It was also found subsequently that the extracted cobs still contained a very large amount of the furfurol-producing bodies. The caustic soda had evidently extracted only a very small amount of the *pentans*, or pentose gums, which accounts for the small yield of sugar. To characterise the product thus obtained, the specific rotation was determined, and its phenyl-hydrazine derivative prepared. Of the two portions of crystals, No. 1 showed the specific rotation $(a)_D = 19.4°$; No. 2, $(a)_D = 19.7°$. These numbers agree with sufficient accuracy with the specific rotation of xylose—$(a)_D = 18.5°$ to 19°—to identify both products as xylose, and show that this was the only pentose present. The phenyl-hydrazine compound was prepared in the usual way, had a normal appearance and behavior, and showed the melting-point 159°—the approximate melting-point observed for phenyl-xylosazon (156°–160°). In distinction from the phenyl-arabinosazon, which has the same melting-point, this compound was distinctly laevo-rotatory, a property of the xylose derivative as shown by Fischer.[1]

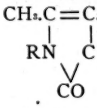
These data add a new and, as we hope to show by a repetition of the above work, a fruitful source of xylose to those already known, and emphasise once more the reliability of the furfurol test for the recognition of such materials.

[1] Ber. d. chem. Ges. **23**, 355.

ON THE ACTION OF AMMONIA AND ANILINE ON α-ACETO-GLUTARIC ETHER.

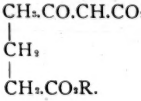
By William Orren Emery.

In a recent paper[1] I described a method by which unsaturated γ-lactams of the general formula

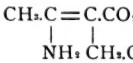


could easily be prepared. It was found that the amido- and alkylamido-derivatives of aceto-succinic ether, under certain conditions, lose the elements of alcohol, and are thereby changed into unsaturated γ-lactams.

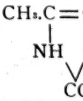
It now seemed desirable to study the action of ammonia and amine bases on some δ-ketonic ether, and to this end I chose α-aceto-glutaric ether,



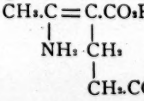
Ammonia and aceto-succinic ether yield α-amido-ethylidene-succinic ether,



which can with comparative ease be changed into the lactam



Now if it were possible by the action of ammonia on α-aceto-glutaric ether to prepare a similar amido-derivative—for example, α-amido-α-ethylidene-glutaric ether,



[1] This Journal **13**, 85.

it might reasonably be expected that such a compound, having the amido-rest in the δ-position to the one carboxyl group, would show even a greater tendency to go over into a lactam. Experiment has shown, however, that such is not the case; only in two instances was it possible, by the action of ammonia and aniline on α-aceto-glutaric ether, to prepare bodies which have apparently the lactam constitution: the intermediate substances formed have not as yet been isolated.

Although the alkyl amines react readily with α-aceto-glutaric ether, I did not succeed in separating the new products in a pure condition, owing to the slight difference between the boiling-points of the latter and of the unchanged ether.

Ammonia and α-Aceto-glutaric Ether.

One volume of α-aceto-glutaric ether was mixed with two volumes of concentrated alcoholic ammonia. After allowing the mixture to stand 24 hours in a cool place, it was poured into a shallow dish, in order that the alcohol might slowly evaporate at the ordinary temperature. As the residual liquid showed no signs of crystallisation, it was next distilled under greatly diminished pressure. After considerable unchanged α-aceto-glutaric ether had passed over, a very small quantity of crystals distilled, or rather sublimed, over, while the residue in the distilling flask crystallised on cooling. The crystals were first freed from an oily substance by drying on porous plates, then recrystallised twice from a mixture of chloroform and ether. Small, white crystals were obtained, which melted at 156°, and upon analysis gave the following figures:

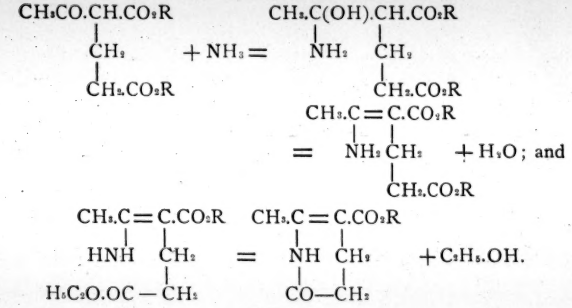
I. 0.1512 gram substance gave 0.3255 gram CO_2 and 0.0963 gram H_2O.

II. 0.2139 gram substance gave the following data: $B = 767.5$; $t = -1.5°$; $v = 13$ cc.

	Calculated for $C_9H_{13}NO_3$.	Found. I.	Found. II.
C	59.02	58.71	...
H	7.10	7.08	...
N	7.65	...	7.71
O	26.23	...	...

The new compound has therefore the formula $C_9H_{13}NO_3$ and

is probably the last product arising by the action of ammonia on α-aceto-glutaric ether, according to the equations



The new substance may be regarded as the lactam of α-amido-α-ethylidene-glutaric ether. It is quite readily soluble in chloroform, less so in ether.

Aniline and α-Aceto-glutaric Ether.

Aniline and α-aceto-glutaric ether were mixed in the proportion of equal molecular-weights. After allowing the mixture to stand for several days, it was distilled in a vacuum. Unchanged aniline and ether passed over, leaving a residue in the distilling-flask; upon treating this residue with ether it gradually solidified to a mass of fine crystals. These were first freed from an accompanying oil by drying on porous plates, then recrystallised twice from a mixture of chloroform and ether. Fine, white crystals were obtained, which melted at 196°–197°, and on analysis gave the following numbers:

I. 0.1406 gram substance gave 0.3586 gram CO_2 and 0.0862 gram H_2O.

II. 0.2640 gram substance gave the following data: $B=761$; $t=7°$; $v=13$ cc.

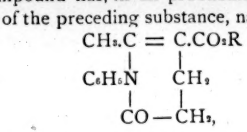
	Calculated for $C_{12}H_{17}NO_3$.	Found.	
C	69.50	69.55	...
H	6.56	6.81	...
N	5.40	...	5.97
O	18.53	...	...

From the above it is evident that the new substance is formed

from equal molecules of aniline and α-aceto-glutaric ether, according to the equation

$$C_{11}H_{18}O_5 + C_6H_5.NH_2 = C_{15}H_{17}NO_3 + H_2O + C_3H_6O.$$

The new compound has, in all probability, a constitution analogous to that of the preceding substance, namely—



and may be regarded as the lactam of α-phenyl-amido-α-ethylidene-glutaric ether. It is easily soluble in chloroform; with difficulty in ether.

CHEMICAL LABORATORY, BONN UNIVERSITY, *February*, 1891.

THE ATOMIC WEIGHT OF OXYGEN.

BY W. A. NOYES.

In a recent number of this Journal[1] Dr. E. H. Keiser has pointed out a source of error in my determinations of the atomic-weight of oxygen. In order to determine how far the error in question can have affected the result which was obtained, the following experiments have been made:

Ten grams of caustic potash, from the same dealer and of the same grade as that used in my work last year, were placed in a small bulb, which was then sealed to a tube bearing a stop-cock. To the other end of the tube was sealed a second bulb, which could be connected with a Sprengel pump. The whole was then exhausted and the stop-cock closed. Twelve to fifteen cubic centimeters of water were placed in the upper bulb and the latter was again exhausted. By continuing the action of the pump at intervals for one or two hours, most of the air dissolved in the water was removed. On opening the stop-cock the water ran down into the bulb containing the caustic potash. The gases evolved by the solution of the latter in the water were pumped out and analysed. They consisted in one experiment of 0.42 mg. of nitrogen and 0.10 mg. of oxygen; in a second experiment, of 0.63 mg. of nitrogen and 0.16 mg. of oxygen.

[1] This Journal **13**, 253.

From the amount of caustic potash used in my drying tubes, it is impossible that more than three or four grams of caustic potash could have passed into solution in the course of any single determination. It seems to be certain, therefore, that the amount of oxygen from this source could not have exceeded, on the average, one-tenth of a milligram for each determination, and was probably decidedly less than that. One-tenth of a milligram of oxygen, if present, would cause an error of 0.002 H in my final result, or, if a correction were applied, it would raise the value from 15.896 to 15.898.

It may be remarked, further, that the fact that the oxygen coming from the caustic potash is always associated with several times its weight of nitrogen, taken in connection with the amounts of nitrogen which were found in my hydrogen, proves that the hydrogen could not have been seriously contaminated from this source.

Dr. Keiser suggests that there are other sources of error in my work. I am well aware that this is the case, and I sincerely hope that errors which I may have overlooked, or whose importance I may have underestimated, may be pointed out. My desire is the same as that of all other chemists—that we may soon have an accurate and established value for the constant in question.

It is with extreme reluctance that I refer at all to the remarks with which Dr. Keiser opens his communication. Morley has shown that dry air can not be passed through a rubber connection without taking up water. In the sketch of his apparatus which Dr. Keiser has given,[1] he represents the oxygen and air as passing through several inches of rubber tubing before entering the phosphorus pentoxide tube to which I have referred. It would seem, then, not a transgression of the truth to say that an error must have been introduced when the assumption was made that *all* of the gain in weight of that tube came from water in the hydrogen which was passed through it. It is entirely possible that I have overestimated the importance of this error. The only positive statement which I had made, however, is that an error has been pointed out; even that statement was qualified in one of the papers which have been referred to by Dr. Keiser.

Rose Polytechnic Institute, *April*, 1891.

[1] Am. Jour. of Sci. **34**, 200.

REVIEWS AND REPORTS.

The Isomeric Benzene Hexachlorides.[1]

Before considering the two articles by Friedel and by Matthews which call forth this article, a brief review of the literature of the subject may not be out of place.

The ordinary benzene hexachloride, $C_6H_6Cl_6$, was first studied by Faraday and by Mitscherlich, and is a substance crystallising in clinorhombic prisms and fusing at 157°. In 1884 Meunier[2] found that benzene hexachloride formed by the action of chlorine on boiling benzene in the sunlight, contains a small amount of an isomer fusing and subliming at about 310°, and crystallising in regular octahedra. In the same year Schüpphaus[3] published an article in which he showed that he had obtained the same substance somewhat before Meunier, but had supposed it to be diphenyl dodekachloride, $C_{12}H_{10}Cl_{12}$. Schüpphaus gave his crystals to Dr. H. Söffing for crystallographic examination; they were found to be regular octahedra, and identical with the substance obtained by Meunier. Paterno and Nasini[4] in 1888 determined the molecular-weight of the two chlorides by Raoult's method, and found both to have the formula $C_6H_6Cl_6$.

Matthews, in the paper referred to, in studying the simultaneous action of chlorine and sodium hydroxide on organic compounds, found that when chlorine is conducted into a 1-per cent. solution of sodium hydroxide on which benzene is floating, the benzene is converted into a heavy yellow oil, which in a few hours deposits colorless crystals, and on further treatment with chlorine is almost completely changed to benzene hexachloride. He finds that the presence of the sodium hydroxide increases the yield of hexachloride, equally good results being obtained in sunlight or darkness. When recrystallised several times from 80-per cent. acetic acid, the substance fuses at 157°, but a portion is left unfused; he recognises in this Meunier's β-chloride, and tries various methods of separation, among others Meunier's, which consists in boiling the crude chloride with alcoholic potassium cyanide for 30 hours. This treatment completely decomposes the α-compound and does not decompose the more stable β-chloride, which is extracted with alcohol and purified by sublimation. Matthews finally found that if the crude chlorides be distilled in a current of steam, the α-chloride is volatile, the β- remains behind: the separation is complete. On

[1] C. Friedel: Sur les hexachlorures de benzène; Bull. Soc. chim. (Paris) [3] **5**, 130. F. E. Matthews: The α- and β-Modifications of Benzene Hexachloride; J. Chem. Soc. 1891, 165.
[2] Meunier: Bull. Soc. chim (Paris) [2] **41**, 530.
[3] Schüpphaus Ber. d. chem. Ges. **17**, 2256.
[4] Gazz. chim. ital. **19**, 195; reviewed in Ber. d. chem. Ges. **22**, Referate, 643-4.

recrystallising the β-derivative a single time from alcohol, he finds it pure; the α-derivative recrystallised from alcohol or acetic acid is also found to be quite pure and free of the β-. He shows the α-chloride to be insoluble in water, easily soluble in ordinary organic solvents; very stable—not acted on by fuming nitric acid, chromic acid, ammonia, or boiling silver nitrate—; alcoholic potash and potassium cyanide decompose it; when heated above its melting-point it loses hydrochloric acid. The molecular-weight determination by Raoult's method confirmed the results of Paterno. The α-chloride forms about 70 per cent. of the crude chlorides.

The β-modification is extremely stable. Boiling alcoholic potassium cyanide does not affect it; it must be boiled for three hours with alcoholic potash to insure decomposition; it is much less soluble than the α-, but the two cannot be separated satisfactorily by fractional crystallisation. The molecular-weight determination (Raoult) gives the formula $C_6H_6Cl_6$, as found by Paterno. Both modifications, boiled with alcoholic potash, yield the same trichlor-benzene.

While Matthews has increased our knowledge of the subject, through his improved method of making the crude hexachlorides and his quantitative separation of the two modifications, M. Friedel in his paper discusses in a remarkably ingenious way the constitution of the two hexachlorides, in the light of the stereochemical hypothesis. The paper is closely condensed, and it seems best in some parts of it simply to translate the author's words. He refers first to the application of Le Bel and Van't Hoff's theory to Kekulé's benzene-formula, by which, supposing that the simple union of two carbon atoms is expressed by the contact of two tetrahedra at an apex of each, and that double union of two carbon atoms is expressed by the coincidence of an edge of each of two tetrahedra, we obtain a figure like the following:

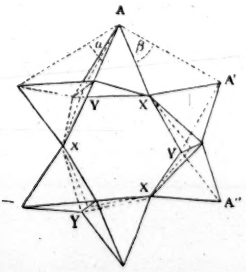


FIG. 1.

Friedel thinks that the well-known objection made to the Kekulé formula—that it admits the possibility of two ortho-derivatives of benzene—can be disposed of by the very simple assumption that the action of an atom of hydrogen—or of a group replacing it—on other atoms depends on the *distance*, all other conditions being equal. Now, in benzene, according to the Kekulé formula, each atom of hydrogen is joined to an atom of carbon, which is itself joined by one valence to an exactly similar atom of carbon, and by two valences to another; the hydrogen atoms are then in exactly the same conditions, and it seems fair to assume that if the *distances* separating them, *i. e.*, the distances between the free apices of the tetrahedra, are *equal*, the reciprocal action will be equal.

It is easy to satisfy this condition in a figure formed by three groups of two tetrahedra each—the two tetrahedra having a common edge, and each group being united to the two other groups by one valence; this being Kekulé's formula merely expressed stereo-chemically.

Calculation shows that the free apices of the tetrahedra will be equidistant when the edges of the hexagon formed by joining these apices form with those edges of the tetrahedra lying in the same plane the angles $\beta = 39° 1' 58''$; and when the intersections of the same plane with those exterior faces of the tetrahedra normal to the plane P form the angles $\alpha = 26° 14'$ (Fig. 1). In this case the angles of the symmetric hexagon formed by the intersections of the plane containing the free apices of the tetrahedra, with the interior faces of the tetrahedra normal to this plane, will be 148° 36′ at the angles XXX, where there is simple union, and 91° 24′ at the points YYY, where there is double union. A figure of this kind satisfies the conditions demanded, *i. e.*, *equal distances between the atoms of hydrogen*, each of which is otherwise under exactly similar conditions. If this be granted, there is no possibility for the formation of two ortho-derivatives of benzene.

The figure thus obtained is one of great symmetry, and it should be noticed that the successive tetrahedra deviate but little from the position which would be normal in the case of two tetrahedra joined by simple union, inasmuch as the line which would seem to be the line of attraction for two tetrahedra united by an apex—that is, by simple union—is that which passes from the apices to the centres of gravity of the bases, *i. e.*, the lines of the ternary axes of the cube, which form with the edges of the tetrahedron angles of 35° 16′. The deviation from this line in our figure is but 3° 16′ for each of the tetrahedra.

With the double bonds, the attractive force would be exercised in the plane bisecting the dihedral angles of two tetrahedra united by a common edge. The deviation is here a little greater, *i. e.*, 9° for each tetrahedron. These deviations are but trifling in relation to so nearly perfect a symmetry.

Assuming this symbol for benzene, it is easy to see that in the formation of addition-products the double bond will be broken, as in the fatty series, and that in consequence, on adding two atoms of chlorine, those edges of the two tetrahedra which were in contact will fall into the plane which passes through the simple bonds, while those edges which bear each one atom of hydrogen and one atom of chlorine will fall at a right angle to this plane, in such manner that the two chlorine atoms are on the same side of the plane—in the *cis* position, to adopt Bayer's terminology.

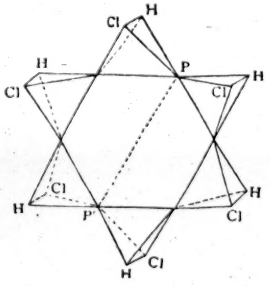


FIG. 2.

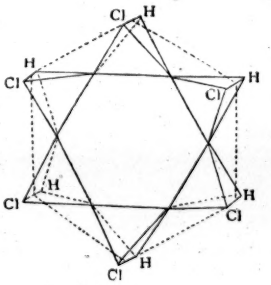


FIG. 3.

Following out this reasoning, we see that only two compounds can be formed by adding three molecules of chlorine to benzene, one *trans*, the other *cis*, as shown in Figs. 2 and 3. In the *trans*, four atoms of chlorine, attached to four adjacent carbon atoms, are on one side of the plane of the molecule, and the two other atoms on the other side.

It is to be noted that, supposing nothing causes the double bond to break preferably on one or the other side of the plane, there will always be one part of the *cis* isomer formed to three parts of the *trans*. For, after the first molecule of chlorine is fixed, the second may be placed on the same side of the plane, or on the other; and, other conditions being equal, will yield as much tetrachloride of the *cis* as of the *trans* modification. The *third* molecule of chlorine, reacting with the *cis* tetrachloride, will form as much hexachloride of the *cis* as of the *trans* variety, but, reacting with the *trans* tetrachloride, it can form only the *trans* hexachloride;—or, summed up, *one* part *cis* to *three* parts *trans*.

Of course these conclusions—which would hold strictly if the products formed by the action of chlorine were enantiomorphous, differing only in rotatory power—cannot hold strictly where, as in the present case, the isomeric bodies differ greatly, both in their structure and properties. Still, the action of chlorine on the interme-

diate products formed may sometimes be very slight, so that this reasoning may give an approximate idea of what takes place. M. Friedel goes on to say that he has obtained from the crude hexachloride—by fractional crystallisation with chloroform—1 part of octahedric hexachloride to 4 or to 3½ parts of the clinorhombic modification. It will be remembered that Matthews, by his better method of separation, obtained 70 per cent. α- to 30 per cent. β-, which is still nearer to the proportion suggested by Friedel. The latter argues that the octahedral β-modification is *cis* because of the proportion in which it is formed, and because the greater symmetry of the *cis* structure may account for the comparative stability, greater density, and higher boiling-point of the octahedral variety.

Friedel thinks that the coincidence in these substances between the crystalline symmetry and the molecular symmetry cannot be accidental, for, on examining Fig. 2, it will be seen that the molecule of the α-hexachloride has a clinorhombic symmetry, and admits of only one plane of symmetry, the trace of which on the plane of the simple bonds is PP' to which the one axis of symmetry is perpendicular: the α-hexachloride crystallises in clinorhombic prisms.

Meunier described his hexachloride as crystallising in regular octahedra without action on polarised light. It is true that, when it is crystallised from benzene or chloroform, octahedra having exactly the appearance and angles of regular octahedra are formed; but M. Friedel finds by careful study that these octahedra are made up by grouping eight pyramids having for bases the faces of the octahedra, their apices being united in the centre of the crystal. He finds that these crystals act on polarised light; he considers it certain that they belong in the category of the pseudo-regular substances studied by Mallard, where the octahedra are formed by grouping eight triangular pyramids belonging to the rhombohedric or hexagonal system.

Now, as shown in Fig. 3, the symmetry of the molecule of the β-benzene hexachloride is, as is suggested by a consideration of his hypothesis, an hexagonal symmetry.

E. Renouf.

CORRECTION.

Page 160, No. 3, line 13 from bottom: *After* "β-ethoxy-naphthalene" *insert* "Thirty grams of the β-diazo-naphthalene sulphate yielded six grams of β-ethoxy-naphthalene and only one gram of naphthalene, which is equivalent to a conversion of about thirty per cent. of the diazo compound into β-ethoxy-naphthalene, and seven per cent. into naphthalene."